



ANTISENSE RNA WITH A SECONDARY STRUCTURE

The present invention concerns antisense RNA with a secondary structure, a kit comprising the same, as well as the use of both.

New techniques to inhibit gene expression comprise often the use of antisense RNA. This is an RNA which is complementary to a region of a mRNA of a gene, and binds this domain. A duplex molecule is formed which cannot be translated. In this way an inhibition of gene expression can be achieved.

It has been shown that the duplex molecule is often not stable, i.e. the mRNA becomes available again for translation, resulting in an inhibition of the gene expression which is weak or not existing at all.

The basis of the present invention is to provide a means for strong inhibition of gene expression.

According to the invention, this is achieved by providing a antisense RNA with special secondary structures.

By the term "special secondary structure" is meant that the structure is not a naturally occurring secondary structure, but that it has been artificially produced.

The term "Antisense RNA" comprises each RNA molecule which can be used as an antisense RNA, i.e. which is complementary to a region of an RNA, preferably mRNA and particular regulatory elements thereof and by binding this region causes inhibition of gene expression. The antisense RNA can also comprise DNA sequences. Further the antisense RNA may be used as such or in the form of a vector encoding the antisense RNA. Such a vector may be an overexpression vector.

It may be advantageous when the Expression of the sequence coding for the antisense RNA is under the control of a constitutive or inducible promoter, such as a tissue- or tumor-specific promoter.

The term "secondary structure" comprises each DNA and/or RNA sequence which is present in an antisense RNA, and at least has partially a "hairpin" structure, i.e. individual basepairs are susceptible to backfolding. The secondary structure may be present within the antisense RNA. Also it may be present at the 5' and/or 3' end of the antisense RNA. If more than one secondary structure is present, they may be identical or different from each other. Preferentially the secondary structure is a (GC) n -palindrome-(GC) n sequence, a (AT) n -palindrome-(AT) n sequence, or a (CG) n -palindrome-(CG) n sequence, whereby it is particularly preferred that $n=20$ and the palindrome is a EcoRI restriction site. Preferred are also complex palindromes such as (AGCT) n or (GAATTC) n .

Antisense RNA according to the invention can be made according to common methods. It may be advantageous to produce a double stranded (GC) $_{20}$ -EcoRI-(GC) $_{20}$ sequence by oligonucleotide synthesis and to ligate this to the 5' end of a cDNA sequence of the gene to be silenced. The resulting DNA molecule can be ligated in the 3'->5' direction to the promoter of a vector. The obtained vector results in expression of the antisense RNA according to the invention. For completeness, reference is made to Sambrook, Fritsch, Maniatis, A Laboratory Manual, Cold Spring Harbor Laboratory Press, 1989.

The antisense RNA according to the invention can be introduced as such or in the form of a vector encoding same into cells. The cells may be any cells, such as plant cells or animal cells, particularly mammalian cells or more particularly human cells. The cells may be within an organism or outside an organism. The latter may be freshly isolated or maintained as a culture. The introduction of antisense RNA in the cells can be obtained via conventional transfection techniques such as electroporation.

A further embodiment of the present invention is a kit of the antisense according to the invention and a (ds)RNase. This is an RNase which recognizes and degrades double stranded RNA. A (ds)RNase is present e.g. in the yeast strain *Schizosaccharomyces pombe* (pac 1+). In the kit the antisense RNA according to the invention may be present as such or in the form of a vector encoding the same. Also, the (ds)RNase may be present as such or in the form of a vector encoding the same. Such a vector may be a conventional expression vector. It may be advantageous that expression of the sequence coding for the (ds)RNase is under the control of a constitutive or inducible promoter, such as a tissue- or tumor specific promoter. Further it may be an advantage if the kit comprises a vector encoding both the antisense RNA according to the invention and the (ds)RNase. With respect to the vector reference is made to above mentioned embodiments.

The combination of the antisense RNA according to the invention and the dsRNase may be introduced into cells. With respect to the cells and the introduction of the antisense RNA according to the invention into cells, reference is made to the above mentioned embodiments. The (ds) RNase can be introduced as such, i.e. as a protein, using conventional methods such as lipofection. In the form of a vector encoding a (ds)RNase it may be introduced using a method as mentioned for introduction of the antisense RNA.

The present invention provides an antisense RNA and a kit comprising the same, which bring about a strong inhibition of gene expression. The present invention has broad application in molecular biology and medicine. In particular, diagnosis and/or therapy of diseases caused or intensified by single proteins may be envisaged. These are e.g. diseases wherein hormones play a major role, cancer and viral infections, such as HIV and AIDS.

Brief description of the drawings

Fig. 1 shows the inhibition of gene expression by an antisense RNA according to the invention. (1) is the expression rate of a CAT gene in the presence of an antisense RNA. (2) is the expression rate of a CAT gene in the presence of an antisense RNA having secondary structure I. (3) is the expression rate of a CAT gene in the presence of an antisense RNA having secondary structure II.

Fig. 2 shows the inhibition of gene expression by an antisense RNA according to the invention. (1) is the expression rate of a CAT gene in the presence of an antisense RNA with secondary structure I (2) is the expression rate of a CAT gene in the presence of an antisense RNA with secondary structure I and a (ds)RNase.

The invention is illustrated by the following Examples.

Example 1: Construction of Expression vectors comprising the chloramphenicolacetyl transferase (CAT) gene in 5'→3' respectively 3'→5' direction.

The CAT -gene was isolated from a conventional CAT vector and inserted into the "multiple cloning site" of the expression vector pJ3Ω (cfr. Nucleic Acids Res. 18 (1990), 1068). In one case the insertion occurred in the 5'→3' direction and expression vector pJ3Ω-CAT was obtained. In the other case the insertion occurred in the 3'→5' direction and expression vector pJ3Ω-TAC was obtained.

Example 2: Construction of expression vectors comprising the CAT gene in 3'→5' direction and a sequence encoding secondary structure I, respectively II.

(A) Expression vector with a (GC)₂₀-EcoRI-(GC)₂₀ sequence at the 5' end of the CAT gene (secondary structure I)

1. Construction of the (GC)₂₀-EcoRI-(GC)₂₀ sequence.

(a) Using a automatic synthesis machine (oligonucleotid synthesizer) 2 oligodesoxynucleotides were made:

AATTC- (GC)₂₀-G

And

G- (GC)₂₀-CTTAA

(b) Both oligodesoxynucleotides were mixed in a ratio 1:1, heated at 90°C, and slowly cooled to room temperature under "annealing" conditions. This resulted in a doublestranded DNA of the following structure.

AATTC- (GC)₂₀-G

* * *

G- (GC)₂₀-CTTAA

(c) Under ligation conditions multimers of the DNA described under (b) were obtained

AATTC- (GC)₂₀-GAATTC- (GC)₂₀-GAATTC- (GC)₂₀-G.

* * * * * * *

G- (GC)₂₀-CTTAAG- (GC)₂₀-CTTAAG- (GC)₂₀-CTTAA.

(d) The ligation products were separated according to size by gel electrophoresis

and a sequence consisting of dimers was eluted from the gel and phosphorylated using polynucleotide kinase/ATP

AATTC- (GC)₂₀-GAATTC- (GC)₂₀-G-P
 * ** * *

P- G- (GC)₂₀-CTTAAG- (GC)₂₀-C

- (e) Next, this sequence was inserted into the EcoRI site of the commonly used cloning vector pBluescript (Stratagene), from which the sequence could be isolated using appropriate restriction enzymes for recloning in the vector comprising the CAT gene in the 3'-5' orientation.

2. Introduction of the (GC)₂₀-EcoRI-(GC)₂₀ sequence in the vector containing the CAT gene in the 3' to 5' direction.

The vector pJ3Ω-TAC from Example 1 was digested with appropriate restriction enzymes in the "multiple cloning site" between the promoter and the TAC-insertion. The (GC)₂₀-EcoRI-(GC)₂₀ sequence was isolated with the corresponding enzymes from the pBluescript vector of example 2(e). Both nucleic acids were annealed by ligation. The expression vector pJ3Ω-TAC-Sek.I was thus obtained.

(B) Expression vector with a (GC)₂₀-EcoRI-(GC)₂₀ sequence at the 3' end of the CAT gene (secondary structure II).

The (GC)₂₀-EcoRI-(GC)₂₀ sequence from example 2(A) was introduced into the vector pJ3Ω-TAC at the 3' end of the TAC-gene. The expression vector pJ3Ω-TAC-Sek.II was thus obtained.

Exempl 3. Construction of an expression vector encoding a (ds)RNase.

The gene (pac 1+) encoding a (ds)RNase was isolated by PCR-amplification from a common genomic library of *Schizosaccharomyces pombe*. To this end, primers were used which were derived from the known sequence of the pac 1+ gene (cfr database: EMBL:S78982). The gene pac 1+ was cloned in the known vector pBluescript and confirmed by DNA sequence analysis. After recloning in the conventional expression vector pcDNA3 (Invitrogen) the expression vector pcDNA3-pac1+ was obtained.

Example 4: Inhibition of gene expression by an antisense RNA with secondary structure.

- (a) Ehrlich Ascites tumor cells (10^7 cells/ml) were transfected with the expression vectors pJ3 Ω -CAT, pJ3 Ω -TAC, pJ3 Ω -TAC-Sek.I and respectively pJ3 Ω -TAC-Sek.II (cfr. Table 1). The transfection was performed by electroporation (366V/9560 μ F/ distance between electrodes D=4mm). 24 hrs after transfection, the cells were harvested, lysed and aliquots were incubated with radioactive labeled chloramphenicol. The conversion rates (to AC- Di-AC-Chloramphenicol) were determined after TLC by measuring radioactivity.

Table I

	1	2	3
pJ3 Ω -CAT	3 μ g	3 μ g	3 μ g
pJ3 Ω -TAC	7.5 μ g	-	-
pJ3 Ω -TAC-Sek.I	-	7.5 μ g	-
pJ3 Ω -TAC-Sek.II	-	-	7.5 μ g

From fig. 1 it can be deduced that a stronger inhibition of the expression of the CAT gene is obtained when pJ3 Ω -TAC-Sek.I, respectively pJ3 Ω -TAC-Sek.II (cfr Fig 1, (2), (3)) is used, than when pJ3 Ω -TAC was used (cfr fig 1, (1)).

(b) Ehrlich Ascites tumor cells (10^7 cells/ml) were transfected with the expression vectors pJ3 Ω -CAT, pJ3 Ω -TAC-Sek.I and respectively pcDNA-3-pac1+ (cfr Table 2). The transfection conditions were as described in Example 4(a).

Table 2:

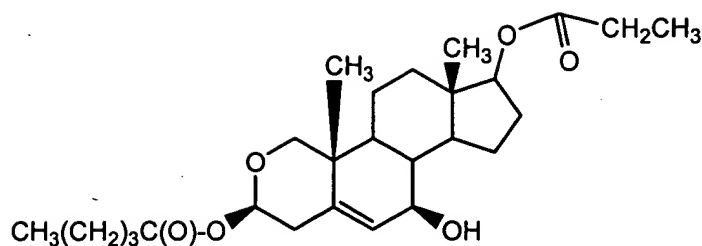
	1	2
pJ3 Ω -CAT	5 μ g	5 μ g
pJ3 Ω -TAC-Sek.I	10 μ g	10 μ g
pcDNA3-pac1+	-	10 μ g

From fig. 2 it can be deduced that a stronger inhibition of the expression of the CAT gene is obtained by cotransfection of pJ3 Ω -TAC-Sek.I and pcDNA3-pac1+ (cfr. Fig 2(2)), as compared to when only pJ3 Ω -TAC-Sek.I (cfr. Fig 2, (1)) is used.

From this it is clear that a antisense RNA with a secondary structure confers a larger inhibition of gene expression than a antisense RNA without secondary structure. Further it becomes clear that the inhibitory activity of the antisense RNA with secondary structure may be enhanced when additionally a (ds)RNAse activity according to the above described methods is produced, in addition to the possibly naturally present (ds)RNAses.

Claims

1. Antisense RNA with special secondary structures.
2. Antisense RNA according to claim 1, characterized in that the secondary structure is created at the 5' and/or the 3' end of the antisense-RNA.
3. Antisense RNA according to claim 1 or 2, characterized in that the secondary structure is a (GC)_n-palindrome-(GC)_n or a (CG)_n-Palindrome-(CG)_n sequence.
4. Antisense RNA according to claim 3, characterized in that n=20 and the palindrome is an EcoRI restriction site.
5. Antisense RNA according to any one of claims 1 to 4, characterized in that the antisense RNA is encoded by a vector.
6. Kit comprising the antisense RNA according to any one of claims 1 to 5 and a (ds)RNase.
7. Kit according to claim 6, characterized in that the antisense RNA and the (ds)RNase are encoded by one or more vectors.
8. Use of the antisense RNA according to any one of claims 1 to 5 and the kit according to claim 6 or 7 for the inhibition of gene expression.



group 28-11-2 compound

1.2.5.9.

Groups 29-1 through 29-25-10-6. These groups comprise each compound named in compound groups 1 through 25-10-6 wherein R⁷ is -NH-, instead of -CH₂-. The compounds are named as described for compound groups 26-1 through 26-25-10-6.

Groups 30-1 through 30-25-10-6. These groups comprise each compound named in compound groups 1 through 25-10-6 wherein R⁸ is -NH-, instead of -CH₂-. The compounds are named as described for compound groups 26-1 through 26-25-10-6.

Groups 31-1 through 31-25-10-6. These groups comprise each compound named in compound groups 1 through 25-10-6 wherein R⁹ is -NH-, instead of -CH₂-. and no double bond is present at the 1-2 position. Thus, there is , e.g., no group 31-3, 31-4, 31-6, 31-8-3, 31-8-4 or 31-8-6. The compounds are named as described for compound groups 26-1 through 26-25-10-6.

Groups 32-1 through 32-25-10-6. These groups comprise each compound named in compound groups 1 through 25-10-6 wherein two of R⁷ R⁸ and R⁹ independently are -NH-, -O- or -S- instead of -CH₂-. The compounds are named as described for compound groups 26-1 through 26-25-10-6.

Groups 33-1 through 33-25-10-6. These groups comprise each compound named in compound groups 1 through 25-10-6 wherein each of R⁷ R⁸ and R⁹ independently are -NH-, -O- or -S- instead of -CH₂-. The compounds are named as described for compound groups 26-1 through 26-25-10-6.

Groups 34-1 through 34-25-10-6. These groups comprise each compound named in compound groups 1 through 25-10-6 wherein R⁷ is -S-, instead of -CH₂-. The compounds are named as described for compound groups 26-1 through 26-25-10-6.

Groups 35-1 through 35-25-10-6. These groups comprise each compound named in compound groups 1 through 25-10-6 wherein R^8 is -S-, instead of -CH₂-. The compounds are named as described for compound groups 26-1 through 26-25-10-6.

Groups 36-1 through 36-25-10-6. These groups comprise each compound named in compound groups 1 through 25-10-6 wherein R^9 is -S-, instead of -CH₂- and no double bond is present at the 1-2 position. There is, e.g., no group 36-3, 36-4, 36-6, 36-8-3, 36-8-4 or 36-8-6. The compounds are named as described for compound groups 26-1 through 26-25-10-6.

Groups 37-1 through 37-25-10-6. These groups comprise each compound named in all of the compound compound groups 1 through 36-25-10-6 described above wherein R^1 is not divalent, e.g., is not =O, and it is in the α -configuration, instead of the β -configuration as shown in formula B.

Groups 38-1 through 38-25-10-6. These groups comprise each compound named in all of the compound groups 1 through 36-25-10-6 described above wherein R^2 is not divalent, e.g., is not =O, and it is in the α -configuration, instead of the β -configuration as shown in formula B.

Groups 39-1 through 39-25-10-6. These groups comprise each compound named in all of the compound groups 1 through 36-25-10-6 described above wherein R^3 is not divalent, e.g., is not =O, and it is in the β -configuration, instead of the α -configuration as shown in formula B.

Groups 40-1 through 40-25-10-6. These groups comprise each compound named in all of the compound groups 1 through 36-25-10-6 described above wherein R^4 is not divalent, e.g., is not =O, and it is in the α -configuration, instead of the β -configuration as shown in formula B. These are thus exemplary formula 2 compounds.

Groups 41-1 through 41-25-10-6. These groups comprise each compound named in all of the compound groups 1 through 36-25-10-6 described above wherein R^2 and R^4 is not divalent, e.g., they is not =O, and they are both in the α -configuration, instead of the β -configuration as shown in formula B.

Groups 42-1 through 42-25-10-6. These groups comprise each compound named in all of the compound groups 1 through 36-25-10-6 described above wherein, when hydrogen is present at the 5-position, it is in the β -configuration, instead of the α -configuration as shown in formula B.

Any of the compounds or genera of compounds that are named in compound groups 1 through 42-25-10-6 are suitable for use in the methods and treating the conditions described herein or in the cited references.

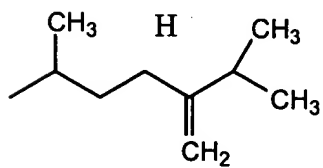
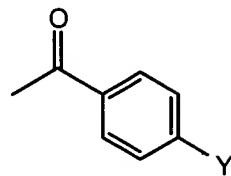
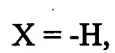
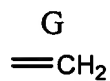
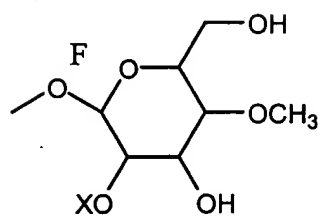
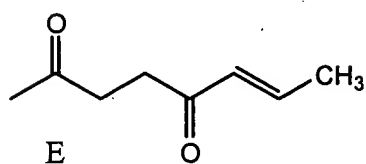
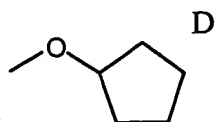
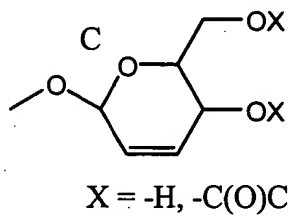
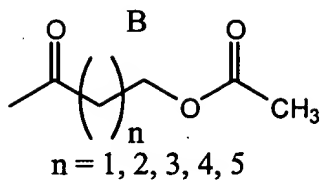
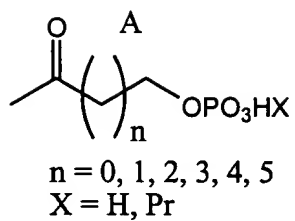
In some embodiments, one, or more of R^1 - R^6 , R^{10} , R^{15} , R^{17} and R^{18} independently have the structure(s) and/or independently comprise the named compounds, -H, -OH, =O, -SH, =S, -NH₂, -CN, -N₃, halogen, =CH₂, =NOH, =NOC(O)CH₃, -C(O)-CH₃, -C(O)-(CH₂)₁₋₄-CH₃, -CCH, -CCCH₃, -CH=CH₂, -CH=CH₂CH₃, -O-C(O)-(CH₂)_m-(CF₂)_n-CH₃, -O-C(O)-(CH₂)_m-(CF₂)_n-CF₃, -O-C(O)-(CH₂)_m-(CF₂)_n-CH₂F, -O-C(O)-O-(CH₂)_m-(CF₂)_n-CH₃, -O-C(O)-O-(CH₂)_m-(CF₂)_n-CF₃, -O-C(O)-O-(CH₂)_m-(CF₂)_n-CH₂F, -O-C(O)-NH-(CH₂)_m-(CF₂)_n-CH₃, -O-C(O)-NH-(CH₂)_m-(CF₂)_n-CF₃, -O-C(O)-NH-(CH₂)_m-(CF₂)_n-CH₂F (where m is 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, usually n is 0), -CH(CH₃)-(CH₂)₂-C(O)NH-CH₂COOH, -CH(CH₃)-(CH₂)₂-C(O)NH-CH₂SO₃H, -OSi(CH₃)₂C(CH₃)₃, -C(OH)=CHCH₃, =CH(CH₂)₀₋₁₅CH₃, -(CH₂)₀₋₁₄CH₂F, -(CH₂)₀₋₁₄CH₂Cl, -(CH₂)₀₋₁₄CH₂Br, -(CH₂)₀₋₁₄CH₂I, -(CH₂)₂₋₁₀-O-(CH₂)₀₋₄CH₃, -(CH₂)₂₋₁₀-S-(CH₂)₀₋₄CH₃, -(CH₂)₂₋₁₀-NH-(CH₂)₀₋₄CH₃, -O-(CH₂)₀₋₁₄CH₂F, -O-(CH₂)₀₋₁₄CH₂Cl, -O-(CH₂)₀₋₁₄CH₂Br, -O-(CH₂)₀₋₁₄CH₂I, -O-(CH₂)₂₋₁₀-O-(CH₂)₀₋₄CH₃, -O-(CH₂)₂₋₁₀-S-(CH₂)₀₋₄CH₃, -O-(CH₂)₂₋₁₀-NH-(CH₂)₀₋₄CH₃, -O-C(O)-(CH₂)₀₋₁₄CH₂F, -O-C(O)-(CH₂)₀₋₁₄CH₂Cl, -O-C(O)-(CH₂)₀₋₁₄CH₂Br, -O-C(O)-(CH₂)₀₋₁₄CH₂I, -O-C(O)-(CH₂)₂₋₁₀-O-(CH₂)₀₋₄CH₃, -O-C(O)-(CH₂)₂₋₁₀-S-(CH₂)₀₋₄CH₃, -O-C(O)-(CH₂)₂₋₁₀-NH-(CH₂)₀₋₄CH₃, -O-C(S)-(CH₂)₀₋₁₄CH₂F, -O-C(S)-(CH₂)₀₋₁₄CH₂Cl, -O-C(S)-(CH₂)₀₋₁₄CH₂Br, -O-C(S)-(CH₂)₀₋₁₄CH₂I, -O-C(S)-(CH₂)₂₋₁₀-O-(CH₂)₀₋₄CH₃, -O-C(S)-(CH₂)₂₋₁₀-S-(CH₂)₀₋₄CH₃, -O-C(S)-(CH₂)₂₋₁₀-NH-(CH₂)₀₋₄CH₃, -(CH₂)₀₋₁₆NH₂, -(CH₂)₀₋₁₅CH₃, -(CH₂)₀₋₁₅CN, -(CH₂)₀₋₁₅CH=CH₂, -(CH₂)₀₋₁₅NHCH(O), -(CH₂)₀₋₁₆NH-(CH₂)₀₋₁₅CH₃, -(CH₂)₀₋₁₅CCH, -(CH₂)₀₋₁₅OC(O)CH₃, -(CH₂)₀₋₁₅OCH(OH)CH₃, -(CH₂)₀₋

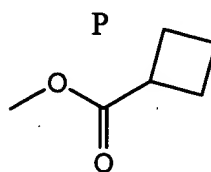
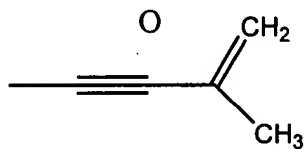
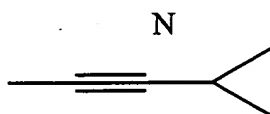
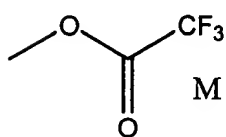
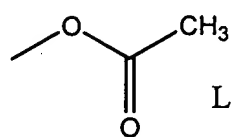
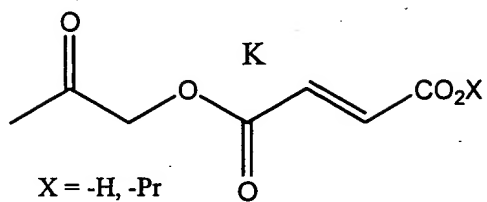
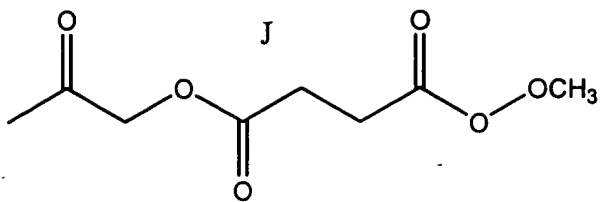
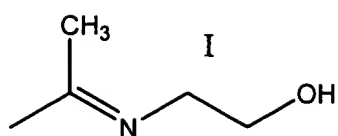
$_{15}\text{C}(\text{O})\text{OCH}_3$, $-(\text{CH}_2)_{0-15}\text{C}(\text{O})\text{OCH}_2\text{CH}_3$, $-(\text{CH}_2)_{0-15}\text{C}(\text{O})(\text{CH}_2)_{0-15}\text{CH}_3$, $-(\text{CH}_2)_{0-15}\text{C}(\text{O})(\text{CH}_2)_{0-15}\text{CH}_2\text{OH}$, $-\text{O}(\text{CH}_2)_{1-16}\text{NH}_2$, $-\text{O}(\text{CH}_2)_{1-15}\text{CH}_3$, $-\text{O}(\text{CH}_2)_{1-15}\text{CN}$, $-\text{O}(\text{CH}_2)_{1-15}\text{CH}=\text{CH}_2$, $-\text{O}(\text{CH}_2)_{1-15}\text{NHCH}(\text{O})$, $-\text{O}(\text{CH}_2)_{1-16}\text{NH}-(\text{CH}_2)_{1-15}\text{CH}_3$, $-\text{O}(\text{CH}_2)_{1-15}\text{CCH}$, $-\text{O}(\text{CH}_2)_{1-15}\text{OC}(\text{O})\text{CH}_3$, $-\text{O}(\text{CH}_2)_{1-15}\text{OCH}(\text{OH})\text{CH}_3$, $-\text{O}(\text{CH}_2)_{1-15}\text{C}(\text{O})\text{OCH}_3$, $-\text{O}(\text{CH}_2)_{1-15}\text{C}(\text{O})\text{OCH}_2\text{CH}_3$, $-\text{O}(\text{CH}_2)_{1-15}\text{C}(\text{O})(\text{CH}_2)_{0-15}\text{CH}_3$, $-\text{O}(\text{CH}_2)_{1-15}\text{C}(\text{O})(\text{CH}_2)_{0-15}\text{CH}_2\text{OH}$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-16}\text{NH}_2$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-15}\text{CH}_3$, $-\text{C}(\text{O})\text{O}(\text{CH}_2)_{1-15}\text{CN}$, $-\text{C}(\text{O})\text{O}(\text{CH}_2)_{1-15}\text{CH}=\text{CH}_2$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-15}\text{NHCH}(\text{O})$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-16}\text{NH}-(\text{CH}_2)_{1-15}\text{CH}_3$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-15}\text{CCH}$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-15}\text{OC}(\text{O})\text{CH}_3$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-15}\text{OCH}(\text{OH})\text{CH}_3$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-15}\text{C}(\text{O})\text{OCH}_3$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-15}\text{C}(\text{O})\text{OCH}_2\text{CH}_3$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-15}\text{C}(\text{O})(\text{CH}_2)_{0-15}\text{CH}_3$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-15}\text{C}(\text{O})(\text{CH}_2)_{0-15}\text{CH}_2\text{OH}$, phosphoenolpyruvate, D-glucosamine, glucolic acid, glucuronic acid, pantothenic acid, pyruvic acid, glucose, fructose, mannose, sucrose, lactose, fucose, rhamnose, galactose, ribose, 2'-deoxyribose, 3'-deoxyribose, glycerol, 3-phosphoglycerate, a PEG (PEG 20, PEG 100, PEG 200, PEG 10000), a polyoxyalkylene polymer, glycine, alanine, phenylalanine, threonine, proline or 4-hydroxyproline.

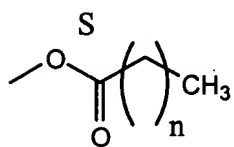
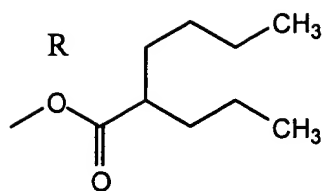
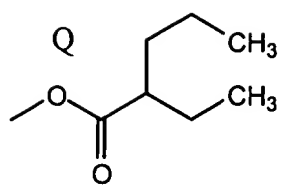
When a substituent is a polymer usually only a one of these is bonded to the formula 1 compound. Typically, when $\text{R}^1\text{-R}^2$ and $\text{R}^4\text{-R}^6$ comprise one or more of these substituents (or others described herein), the substituent is present in the β -configuration, while R^3 typically comprises a substituent in the β -configuration. In some embodiments, R^2 is in the α -configuration.

Table 2 shows exemplary moieties that one or more of $\text{R}^1\text{-R}^6$, R^{10} , R^{15} , R^{17} and R^{18} independently can comprise. Pr means a protecting group. These moieties are often bonded to one or more of the R^1 , R^2 and R^4 positions, usually to one or two of those positions. For structures with more than one of a given variable, e.g., X in structure A3 or A5, each is independently selected.

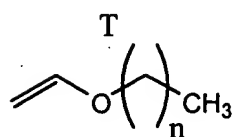
TABLE 2



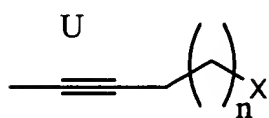




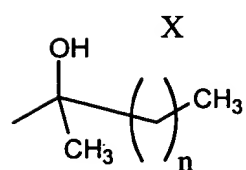
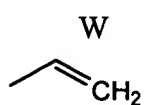
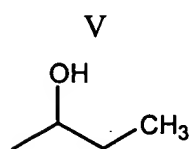
$n = 1, 2, 3, 4, 5, 6$



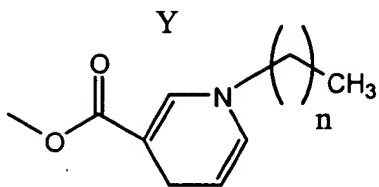
$n = 1, 2, 3, 4, 5, 6$



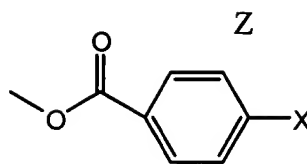
$n = 0, 1, 2, 3, 4, 5, 6$
 $X = \text{CH}_3, \text{Cl}$



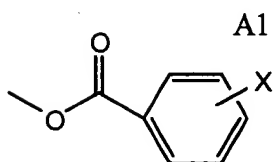
$n = 0, 1, 2, 3, 4, 5, 6$



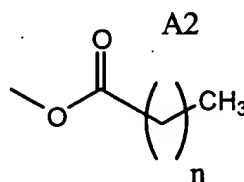
$n = 0, 1, 2, 3, 4, 5, 6$



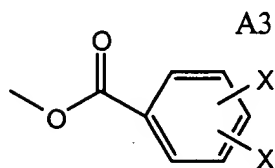
$X = F, Cl, Br, NO_2, OCH_3, OC_2H_5, CN$



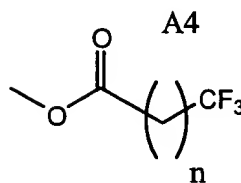
$X = H, F, Cl, Br, NO_2, OCH_3, OC_2H_5, CN$



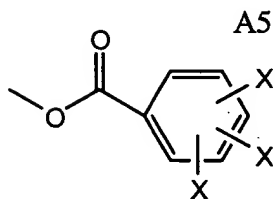
$n = 1, 2, 3, 4, 5, 6$



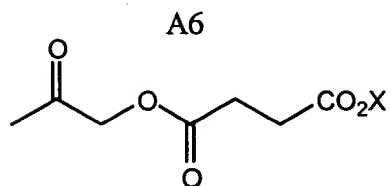
$X = H, F, Cl, Br, NO_2, OCH_3, OC_2H_5, CN$



$n = 0, 1, 2, 3, 4, 5, 6$

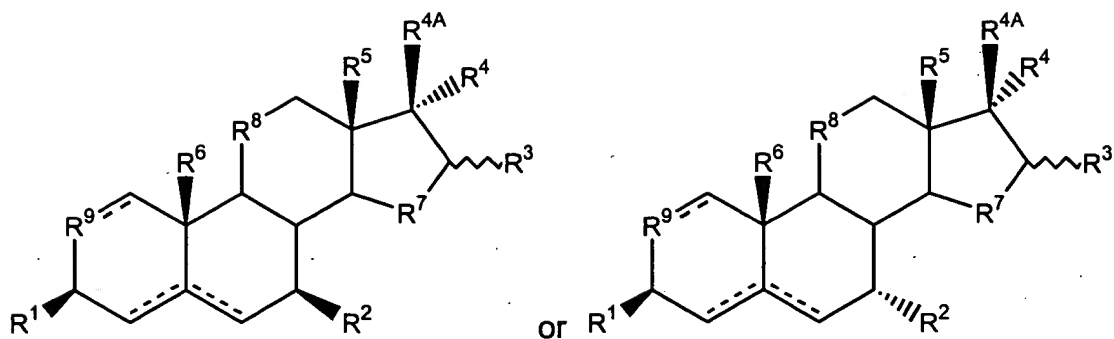


$X = H, F, Cl, Br, NO_2, OCH_3, OC_2H_5, CN$

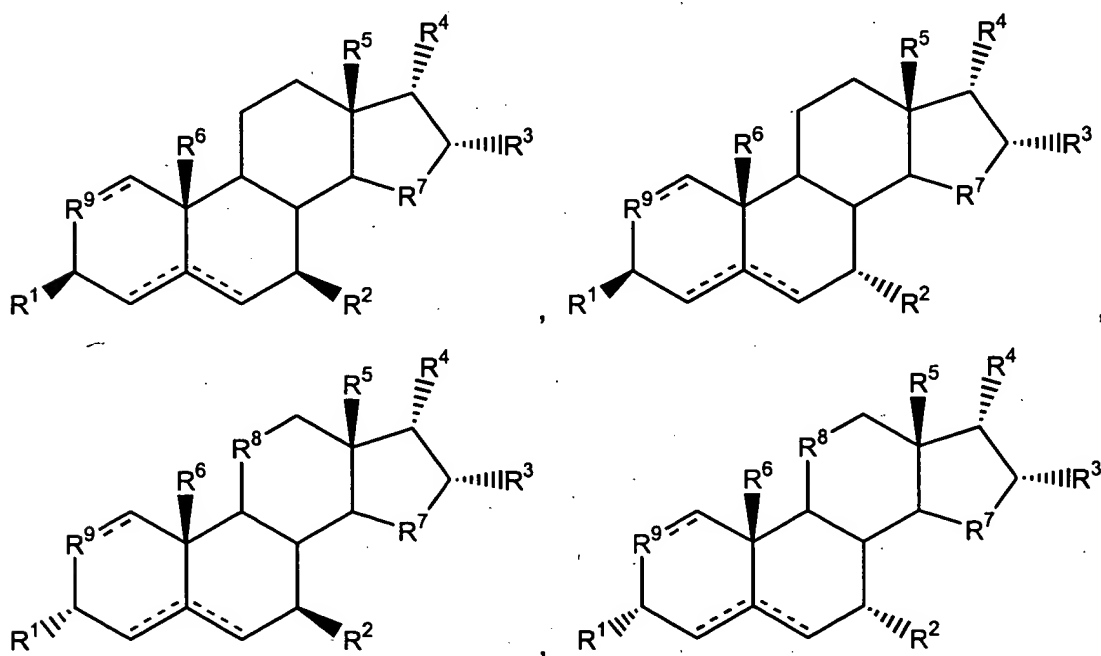


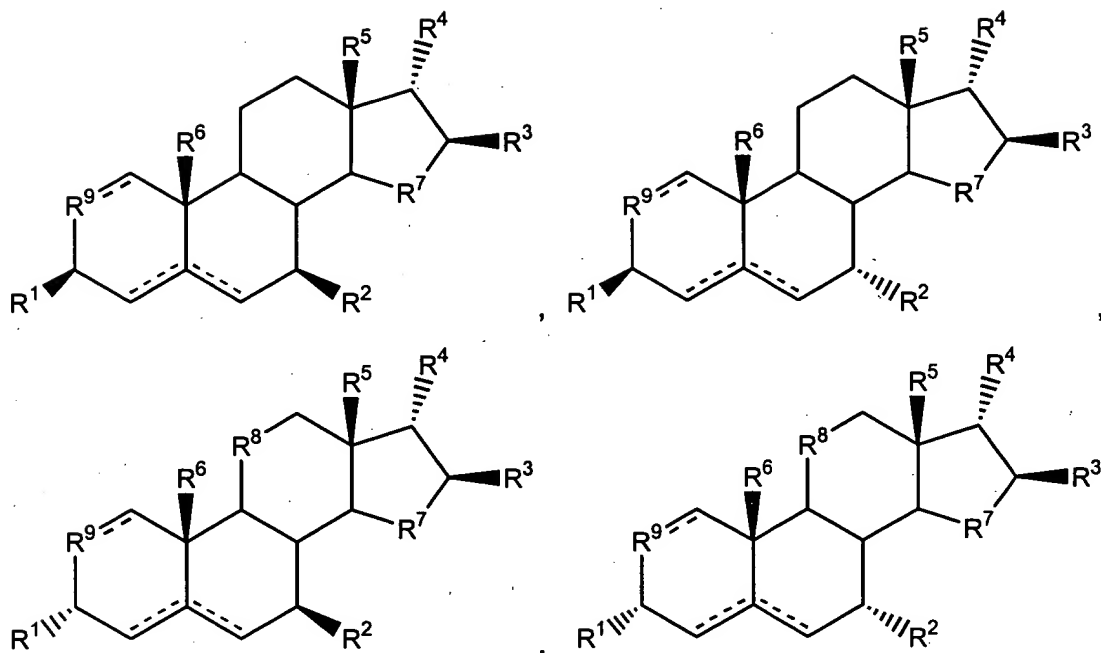
$X = H, Pr$

In some embodiments, the formula 1 compound has the structure



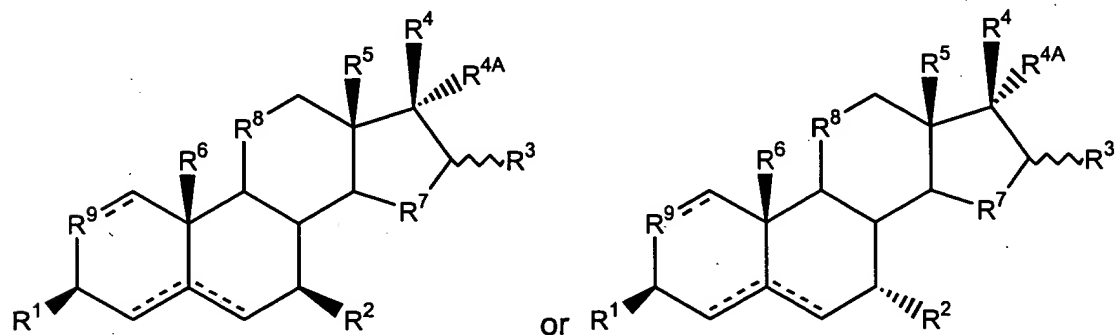
wherein R^{4A} is -H, -CH₃, -C₂H₅ or a halogen, R^7 and R^9 independently are -CHR¹⁰-, -CH₂-, -CH=, -O-, -S- or -NH-, wherein R^{10} is -OH, -SH, C₁₋₁₀ optionally substituted alkyl, C₁₋₁₀ optionally substituted alkoxy and R^8 is -CH₂-, -O-, -S- or -NH-, wherein hydrogen atoms at the 5 (if present), 8, 9 and 14 positions respectively are $\alpha.\alpha.\alpha.\alpha$ (i.e., 5 α , 8 α , 9 α , 14 α), $\alpha.\alpha.\alpha.\beta$, $\alpha.\alpha.\beta.\alpha$, $\alpha.\beta.\alpha.\alpha$, $\beta.\alpha.\alpha.\alpha$, $\alpha.\alpha.\beta.\beta$, $\alpha.\beta.\alpha.\beta$, $\beta.\alpha.\alpha.\beta$, $\beta.\alpha.\beta.\alpha$, $\beta.\beta.\alpha.\alpha$, $\alpha.\beta.\beta.\alpha$, $\alpha.\beta.\beta.\beta$, $\beta.\alpha.\beta.\beta$, $\beta.\beta.\alpha.\beta$, $\beta.\beta.\beta.\alpha$ or $\beta.\beta.\beta.\beta$, typically $\alpha.\alpha.\beta.\alpha$ or $\beta.\alpha.\beta.\alpha$. These compounds include compounds having the structure





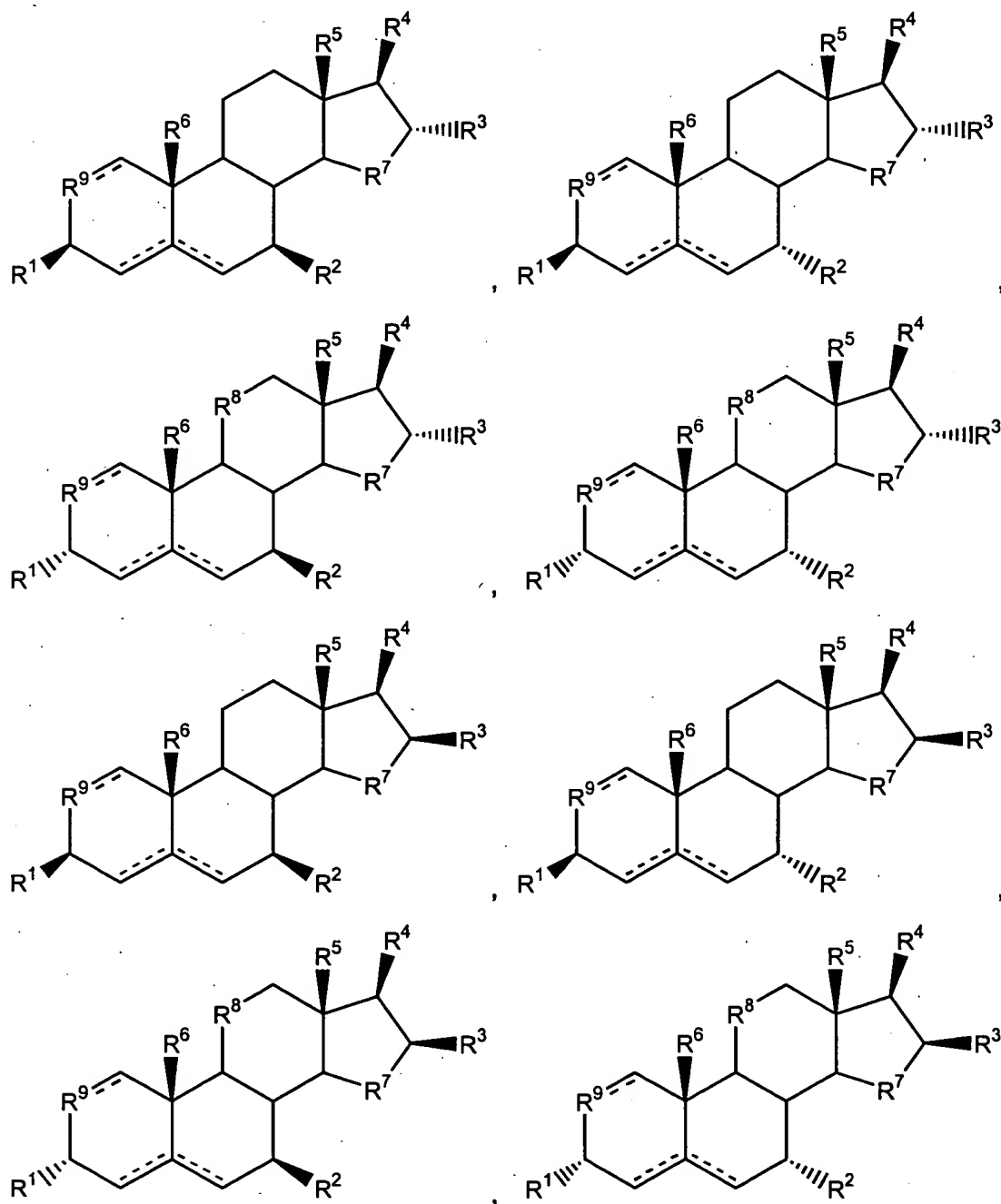
wherein hydrogen atoms at the 5 (if present), 8, 9 and 14 positions respectively are $\alpha.\alpha.\alpha.\alpha$, $\alpha.\alpha.\alpha.\beta$, $\alpha.\alpha.\beta.\alpha$, $\alpha.\beta.\alpha.\alpha$, $\beta.\alpha.\alpha.\alpha$, $\alpha.\alpha.\beta.\beta$, $\alpha.\beta.\alpha.\beta$, $\beta.\alpha.\alpha.\beta$, $\beta.\alpha.\beta.\alpha$, $\beta.\beta.\alpha.\alpha$, $\alpha.\beta.\beta.\alpha$, $\alpha.\beta.\beta.\beta$, $\beta.\alpha.\beta.\beta$, $\beta.\beta.\alpha.\beta$, $\beta.\beta.\beta.\alpha$ or $\beta.\beta.\beta.\beta$, typically $\alpha.\alpha.\beta.\alpha$ or $\beta.\alpha.\beta.\alpha$. In these embodiments, R^1 and R^2 may independently be -OH, -SH, -OR^{PR}, an ester, an ether, a thioester, a thioether or another moiety as disclosed herein, R^3 may be -H, -F, -Cl, -Br, -I, optionally substituted alkyl or another moiety as disclosed herein and R^4 optionally is -OH, -SH or a moiety that can convert to -OH or -SH by metabolism or by hydrolysis, e.g., a moiety as defined herein.

In some embodiments, the formula 2 compound has the structure



wherein R^{4A} is -H, -CH₃, -C₂H₅ or a halogen, R^7 and R^9 independently are -CHR¹⁰-, -CH₂-, -CH=, -O-, -S- or -NH-, wherein R^{10} is -OH, -SH, C₁₋₁₀ optionally substituted alkyl, C₁₋₁₀ optionally substituted alkoxy and R^8 is -CH₂-, -O-, -S- or -

NH-, wherein hydrogen atoms at the 5 (if present), 8, 9 and 14 positions respectively are $\alpha.\alpha.\alpha.\alpha$ (i.e., $5\alpha, 8\alpha, 9\alpha, 14\alpha$), $\alpha.\alpha.\alpha.\beta$, $\alpha.\alpha.\beta.\alpha$, $\alpha.\beta.\alpha.\alpha$, $\beta.\alpha.\alpha.\alpha$, $\alpha.\alpha.\beta.\beta$, $\alpha.\beta.\alpha.\beta$, $\beta.\alpha.\alpha.\beta$, $\beta.\alpha.\beta.\alpha$, $\beta.\beta.\alpha.\alpha$, $\alpha.\beta.\beta.\alpha$, $\alpha.\beta.\beta.\beta$, $\beta.\alpha.\beta.\beta$, $\beta.\beta.\alpha.\beta$, $\beta.\beta.\beta.\alpha$ or $\beta.\beta.\beta.\beta$, typically $\alpha.\alpha.\beta.\alpha$ or $\beta.\alpha.\beta.\alpha$. These compounds include compounds having the structure

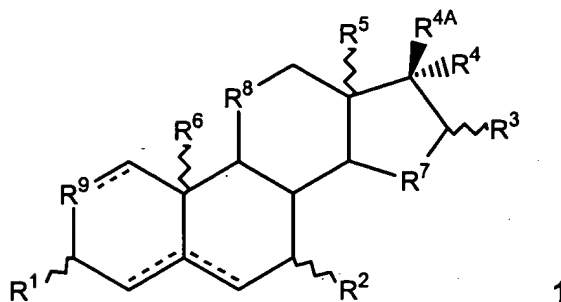


wherein hydrogen atoms at the 5 (if present), 8, 9 and 14 positions respectively are $\alpha.\alpha.\alpha.\alpha$, $\alpha.\alpha.\alpha.\beta$, $\alpha.\alpha.\beta.\alpha$, $\alpha.\beta.\alpha.\alpha$, $\beta.\alpha.\alpha.\alpha$, $\alpha.\alpha.\beta.\beta$, $\alpha.\beta.\alpha.\beta$, $\beta.\alpha.\alpha.\beta$, $\beta.\alpha.\beta.\alpha$,

$\beta.\beta.\alpha.\alpha$, $\alpha.\beta.\beta.\alpha$, $\alpha.\beta.\beta.\beta$, $\beta.\alpha.\beta.\beta$, $\beta.\beta.\alpha.\beta$, $\beta.\beta.\beta.\alpha$ or $\beta.\beta.\beta.\beta$, typically $\alpha.\alpha.\beta.\alpha$ or $\beta.\alpha.\beta.\alpha$. In these embodiments, R^4 may be -OH, =O, -SH, a C_{1-30} ester or C_{1-30} alkoxy, wherein the ester or alkoxy moiety is optionally substituted with one, two or more independently selected substituents, which are optionally selected from -F, -Cl, -Br, -I, -O-, =O, -S-, -NH-, -OR^{PR}, -SR^{PR} or -NHR^{PR}. Also, in these embodiments, R^1 and R^2 may independently optionally be -OH, -SH, -OR^{PR}, an ester, an ether, a thioester, a thioether or another moiety as disclosed herein, R^3 optionally is -H, -F, -Cl, -Br, -I, optionally substituted alkyl or another moiety as disclosed herein and R^4 optionally is -OH, -SH or a moiety that can convert to -OH or -SH by metabolism or by hydrolysis, e.g., a moiety as defined herein.

Compound scop

Compounds of formula 1 (apoptosis inducers) have the structure



wherein,

R^1 , R^2 , R^3 , R^5 , R^6 and R^{10} independently are -H, -OR^{PR}, -SR^{PR}, -N(R^{PR})₂, -O-Si-(R¹³)₃, -CN, -NO₂, F, Cl, Br, I, an ester, a thioester, a phosphoester, a phosphothioester, a phosphonoester, a phosphiniester, a sulfite ester, a sulfate ester, an amide, an amino acid, a peptide, an ether, a thioether, an acyl group, a thioacyl group, a carbonate, a carbamate, a thioacetal, an optionally substituted alkyl group, an optionally substituted aryl moiety, an optionally substituted heteroaryl moiety, an optionally substituted monosaccharide, an optionally substituted oligosaccharide, or a polymer, or,

one more of R^1 , R^2 , R^3 , R^5 , R^6 and R^{10} , are =O or =S and the hydrogen atom that is bonded to the same carbon atom is absent;

R^4 is -OR^{PR}, -OH, -SR^{PR}, -SH, -N(R^{PR})₂, -O-Si-(R¹³)₃, -CN, -NO₂, an ester, a thioester, a phosphoester, a phosphothioester, a phosphonoester, a phosphiniester, a sulfite ester, a sulfate ester, an amide, an amino acid, a peptide, an ether, a thioether, an acyl group, a thioacyl group, a carbonate, a carbamate, a thioacetal, a halogen, an optionally substituted alkyl group, an optionally substituted aryl moiety, an optionally substituted heteroaryl moiety, an optionally substituted monosaccharide, an optionally substituted oligosaccharide or a polymer;

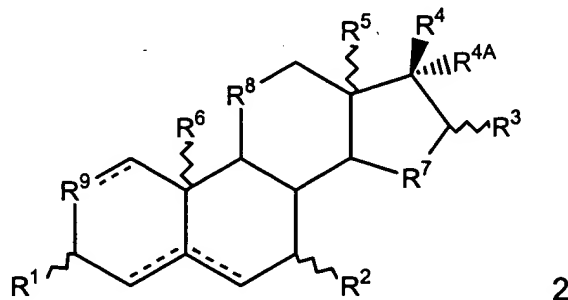
R^{4A} is F, Cl, Br, I, an optionally substituted alkyl group, a heterocycle, an optionally substituted aryl moiety or an optionally substituted heteroaryl moiety;

R^7 is -CHR¹⁰-, -CHR¹⁰-CHR¹⁰-, -CHR¹⁰-CHR¹⁰-CHR¹⁰-, -CHR¹⁰-O-CHR¹⁰-,

-CHR¹⁰-S-CHR¹⁰-, -CHR¹⁰-NR^{PR}-CHR¹⁰-, -O-, -O-CHR¹⁰-, -S-, -S-CHR¹⁰-, -NR^{PR}- or -NR^{PR}-CHR¹⁰-; and

R⁸ and R⁹ independently are -CHR¹⁰-, -CHR¹⁰-CHR¹⁰-, -O-, -O-CHR¹⁰-, -S-, -S-CHR¹⁰-, -NR^{PR}- or -NR^{PR}-CHR¹⁰-, or R⁸ or R⁹ independently is absent, leaving a 5-membered ring.

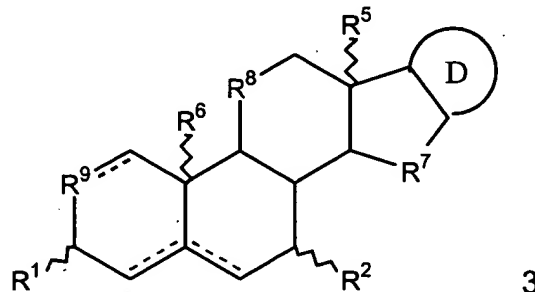
Compounds of formula 2 (immune stimulators) have the structure



wherein R¹, R², R³, R⁴, R^{4A}, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹³ and R¹⁶ are as defined for formula 1 compounds, or

R⁴ and R^{4A} together are =O or =S, or,

R³, R⁴ and R^{4A} together comprise a structure of formula 3



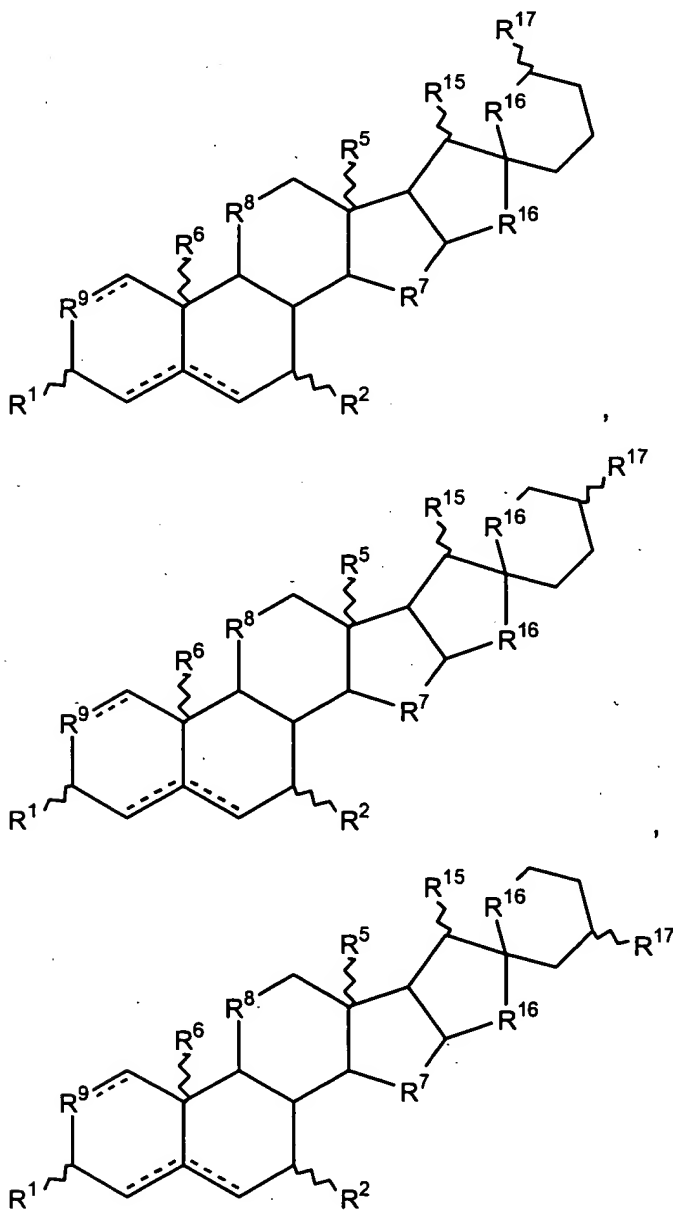
wherein D is a heterocycle or a 4-, 5-, 6- or 7-membered ring that comprises saturated carbon atoms, wherein 1, 2 or 3 ring carbon atoms of the 4-, 5-, 6- or 7-membered ring are optionally independently substituted with -O-, -S- or -NR^{PR}- or where 1, 2 or 3 hydrogen atoms of the heterocycle or where 1 or 2 hydrogen atoms of the 4-, 5-, 6- or 7-membered ring are substituted with -OR^{PR}, -SR^{PR}, -N(R^{PR})₂, -O-Si-(R¹³)₃, -CN, -NO₂, an ester, a thioester, a phosphoester, a phosphothioester, a phosphonoester, a phosphiniester, a sulfite ester, a sulfate ester, an amide, an amino acid, a peptide, an ether, a thioether, an acyl group, a thioacyl group, a carbonate, a carbamate, a thioacetal, a halogen, an optionally

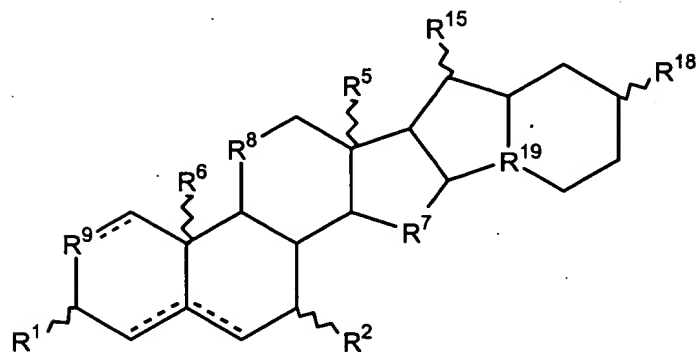
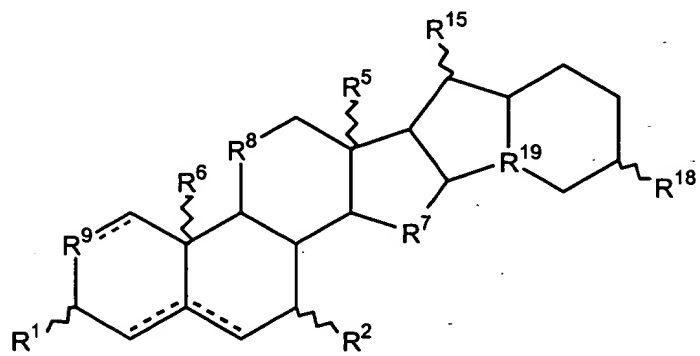
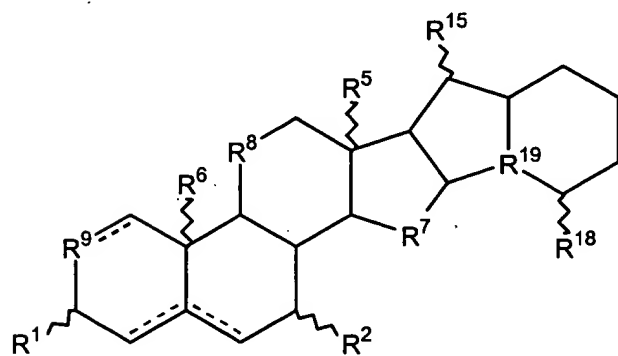
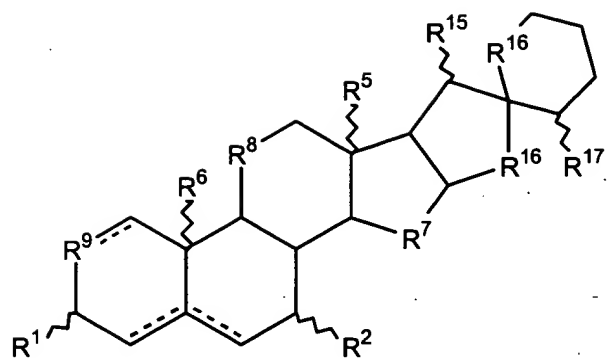
substituted alkyl group, an optionally substituted alkenyl group, an optionally substituted alkynyl group, an optionally substituted aryl moiety, an optionally substituted heteroaryl moiety, an optionally substituted monosaccharide, an optionally substituted oligosaccharide, or a polymer, or,

one more of the ring carbons are substituted with =O or =S,

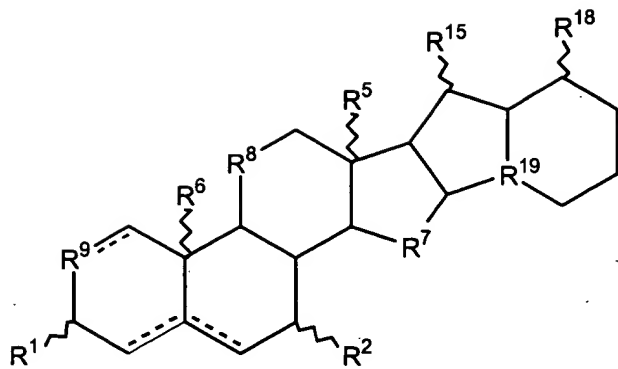
or D comprises two 5- or 6-membered rings, wherein the rings are fused or are linked by 1 or 2 bonds.

Exemplary formula 3 compounds have the structure





or



wherein,

R^{15} , R^{17} and R^{18} independently are -H, $-OR^{PR}$, $-SR^{PR}$, $-N(R^{PR})_2$, $-O-Si-(R^{13})_3$, -CN, $-NO_2$, an ester, a thioester, a phosphoester, a phosphothioester, a phosphonoester, a phosphiniester, a sulfite ester, a sulfate ester, an amide, an amino acid, a peptide, an ether, a thioether, an acyl group, a thioacyl group, a carbonate, a carbamate, a thioacetal, a halogen, an optionally substituted alkyl group, an optionally substituted aryl moiety, an optionally substituted heteroaryl moiety, an optionally substituted monosaccharide, an optionally substituted oligosaccharide, a polymer, or,

one or more of R^{15} , R^{17} and R^{18} independently are =O or =S and the hydrogen atom that is bonded to the same carbon atom is absent, or,

R^{16} independently are $-CH_2-$, $-O-$, $-S-$ or $-NH-$; and

R^{19} is nitrogen or CH.

Definitions

"Heterocycle" or "heterocyclic" includes by way of example and not limitation the heterocycles described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* 1960, 82:5566.

Examples of heterocycles include by way of example and not limitation pyridyl, thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl,

benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinoliny, isoquinoliny, benzimidazolyl, piperidiny, 4-piperidonyl, pyrrolidiny, 2-pyrrolidonyl, pyrroliny, tetrahydrofuranyl, tetrahydroquinoliny, tetrahydroisoquinoliny, decahydroquinoliny, octahydroisoquinoliny, azociny, triaziny, 6H-1,2,5-thiadiaziny, 2H,6H-1,5,2dithiaziny, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiiny, 2H-pyrroly, isothiazolyl, isoxazolyl, pyraziny, pyridaziny, indoliziny, isoindolyl, 3H-indolyl, 1H-indazoly, puriny, 4H-quinoliziny, phthalaziny, naphthyridiny, quinoxaliny, quinazoliny, cinnoliny, pteridiny, 4aH-carbazolyl, carbazolyl, β -carboliny, phenanthridiny, acridiny, pyrimidiny, phenanthroliny, phenaziny, phenothiaziny, furazany, phenoxaziny, isochromany, chromany, imidazolidiny, imidazoliny, pyrazolidiny, pyrazoliny, piperaziny, indoliny, isoindoliny, quinuclidiny, morpholiny, oxazolidiny, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazoliny, and isatinoyl.

By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridaziny, 4-pyridaziny, 5-pyridaziny, 6-pyridaziny, 2-pyrimidiny, 4-pyrimidiny, 5--pyrimidiny, 6-pyrimidiny, 2-pyraziny, 3-pyraziny, 5-pyraziny, 6-pyraziny, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine,

and position 9 of a carbazole, or β -carboline. Typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedy, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

"Heteroaryl" means an aromatic ring or two or more fused rings that contain one or more aromatic rings where the ring or fused rings comprise 1, 2, 3 or more heteroatoms, usually oxygen (-O-), nitrogen (-NX-) or sulfur (-S-) where X is -H, a protecting group or C₁₋₆ alkyl, usually -H. Examples are as described for heterocycle.

"Alcohol" as used herein, usually in the context of excipients, means an alcohol that comprises a C₂₋₁₂ alkyl moiety substituted at a hydrogen atom with one hydroxyl group. Alcohols include ethanol, *n*-propanol, *i*-propanol, *n*-butanol, *i*-butanol, *s*-butanol, *t*-butanol, *n*-pentanol, *i*-pentanol, *n*-hexanol, cyclohexanol, *n*-heptanol, *n*-octanol, *n*-nonanol and *n*-decanol. The carbon atoms in alcohols can be straight, branched or cyclic. Alcohol includes any subset of the foregoing, e.g., C₂₋₄ alcohols (alcohols having 2, 3 or 4 carbon atoms).

"Halogen" means fluorine, chlorine, bromine or iodine.

"Protecting group" means a moiety that prevents the atom to which it is linked from participating in unwanted reactions. For example, for -OR^{PR}, R^{PR} may be hydrogen or a protecting group for the oxygen atom found in a hydroxyl, while for -C(O)-OR^{PR}, R^{PR} may be hydrogen or a carboxyl protecting group, for -SR^{PR}, R^{PR} may be hydrogen or a protecting group for sulfur in thiols for instance, and for -NHR^{PR} or -N(R^{PR})₂, R^{PR} may be hydrogen or a nitrogen atom protecting group for primary or secondary amines. Hydroxyl, amine and other reactive groups are found in formula 1 compounds at, e.g., R¹ or R². These groups may require protection against reactions taking place elsewhere in the molecule. The protecting groups for oxygen, sulfur or nitrogen atoms are usually used to prevent unwanted reactions with electrophilic compounds, such as acylating used, e.g., in steroid chemistry.

"Ester" means a moiety that comprises a -C(O)-O- structure. Typically, esters as used here comprise an organic moiety containing about 1-50 carbon atoms (e.g., about 2-20 carbon atoms) and 0 to about 10

independently selected heteroatoms (e.g., O, S, N, P, Si), where the organic moiety is bonded to a formula 1 steroid nucleus at, e.g., R¹ or R² through the -C(O)-O- structure, e.g., organic moiety-C(O)-O-steroid or organic moiety-O-C(O)-steroid. The organic moiety usually comprises one or more of any of the organic groups described above, e.g., C₁₋₂₀ alkyl moieties, C₂₋₂₀ alkenyl moieties, C₂₋₂₀ alkynyl moieties, aryl moieties, C₂₋₉ heterocycles or substituted derivatives of any of these, e.g., comprising 1, 2, 3, 4 or more substituents, where each substituent is independently chosen. Exemplary substitutions for hydrogen or carbon atoms in these organic groups include 1, 2, 3, 4 or more, usually 1, 2, or 3 -O-, -S-, -NR^{PR}- (including -NH-), -C(O)-, -CHO, -CHS, -C=NH, -C(S), =O, =S, -N(R^{PR})₂ (including -NH₂), -C(O)OR^{PR} (including -C(O)OH), -OC(O)R^{PR} (including -O-C(O)-H), -OR^{PR} (including -OH), -SR^{PR} (including -SH), -NO₂, -CN, -SCN, -C₆H₅, -CH₂C₆H₅, -NHC(O)-, -C(O)NH-, -OC(O)-, -C(O)O-, -O-A8, -S-A8, -C(O)-A8, -OC(O)-A8, -C(O)O-A8, =N-, -N=, =N-OH, -OPO₃(R^{PR})₂, -OSO₃H₂ or halogen moieties or atoms, where each R^{PR} is -H, an independently selected protecting group or both R^{PR} together comprise a protecting group, and A8 is C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkyl-aryl (e.g., benzyl), aryl (e.g. phenyl) or C₀₋₄ alkyl-C₂₋₉ heterocycle. Substitutions are independently chosen. The organic moiety includes compounds defined by the R₄ variable. The organic moieties exclude obviously unstable moieties, e.g., -O-O-, except where such unstable moieties are transient species that one can use to make a compound with sufficient chemical stability for one or more of the uses described herein, including for synthesis of the formula 1 compounds. The substitutions listed above are typically substituents that one can use to replace one or more carbon atoms, e.g., -O- or -C(O)-, or one or more hydrogen atom, e.g., halogen, -NH₂ or -OH.

“Thioester” means a moiety that comprises a -C(S)-O- structure. Typically, thioesters as used here comprise an organic moiety containing about 1-50 carbon atoms (e.g., about 2-20 carbon atoms) and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si), where the organic moiety is bonded to a formula 1 steroid

nucleus at R² through the -C(S)-O- structure, e.g., organic moiety-C(S)-O-steroid or organic moiety-O-C(S)-steroid. The organic moiety is as described above for esters.

"Thioacetal" means a moiety that comprises a -C(O)-S- structure.

Typically, thioacetals as used here comprise an organic moiety containing about 1-50 carbon atoms (e.g., about 2-20 carbon atoms) and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si), where the organic moiety is bonded to a formula 1 steroid nucleus at R² through the -C(O)-S- structure, e.g., organic moiety-C(O)-S-steroid or organic moiety-S-C(O)-steroid. The organic moiety is as described above for esters.

"Phosphoester" or "phosphate ester" means a moiety that comprises a -O-P(OR^{PR})(O)-O- structure where R^{PR} is hydrogen (-H), a protecting group or an organic moiety as described for esters. Typically, phosphoesters as used here comprise a hydrogen atom, a protecting group or an organic moiety containing about 1-50 carbon atoms and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si) linked to a formula 1 steroid nucleus at R¹-R⁶, R¹⁰, R¹⁵, R¹⁷ or R¹⁸ through the -O-P(O)(O)-O- structure, e.g., organic moiety-O-P(O)(OH)-O-steroid. The organic moiety is as described above for esters.

"Phosphothioester" means a moiety that comprises a -O-P(SR^{PR})(O)-O- structure where R^{PR} is -H, a protecting group or an organic moiety as described for esters. Typically, phosphothioesters as used here comprise a hydrogen atom, a protecting group or an organic moiety containing about 1-50 carbon atoms and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si) linked to a formula 1 steroid nucleus at R¹-R⁶, R¹⁰, R¹⁵, R¹⁷ or R¹⁸ through the -O-P(O)(O)-O- structure, e.g., organic moiety-O-P(O)(SH)-O-steroid. The organic moiety is as described above for esters.

"Phosphonoester" means a moiety that comprises a -P(OR^{PR})(O)-O- structure where R^{PR} is -H, a protecting group or an organic moiety as described for esters. Typically, phosphonoesters as used here comprise a hydrogen atom, a protecting group or an organic moiety containing about 1-50 carbon atoms and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si) linked to a formula 1 steroid

nucleus at R¹-R⁶, R¹⁰, R¹⁵, R¹⁷ or R¹⁸ through the -P(OR^{PR})(O)-O- structure, i.e., organic moiety-P(OR^{PR})(O)-O-steroid or steroid-P(OR^{PR})(O)-O-organic moiety. The organic moiety is as described above for esters.

"Phosphiniester" means a moiety that comprises a -P(OR^{PR})-O- structure where R^{PR} is -H, a protecting group or an organic moiety as described for esters. Typically, phosphiniesters as used here comprise a hydrogen atom, a protecting group or an organic moiety containing about 1-50 carbon atoms and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si) linked to a formula 1 steroid nucleus at R¹-R⁶, R¹⁰, R¹⁵, R¹⁷ or R¹⁸ through the -P(OR^{PR})-O- structure, i.e., organic moiety-P(OR^{PR})-O-steroid or steroid-P(OR^{PR})-O-organic moiety. The organic moiety is as described above for esters.

"Sulfate ester" means a moiety that comprises a -O-S(O)(O)-O- structure. Typically, sulfate esters as used here comprise a hydrogen atom, a protecting group or an organic moiety containing about 1-50 carbon atoms and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si) linked to a formula 1 steroid nucleus at R¹-R⁶, R¹⁰, R¹⁵, R¹⁷ or R¹⁸ through the -O-S(O)(O)-O- structure, e.g., organic moiety-O-S(O)(O)-O-steroid. The organic moiety is as described above for esters.

"Sulfite ester" means a moiety that comprises a -O-S(O)-O- structure. Typically, sulfite esters as used here comprise an organic moiety containing about 1-50 carbon atoms and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si) linked to a formula 1 steroid nucleus at R¹-R⁶, R¹⁰, R¹⁵, R¹⁷ or R¹⁸ through the -O-S(O)-O- structure, e.g., organic moiety-O-S(O)-O-steroid. The organic moiety is as described above for esters.

"Thioacetal" means a moiety that comprises a -S-C(O)- structure. Typically, thioacetal groups as used here comprise an organic moiety containing about 1-50 carbon atoms and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si) linked to a formula 1 steroid nucleus at R¹-R⁶, R¹⁰, R¹⁵, R¹⁷ or R¹⁸ through the -S-C(O)- structure, e.g., organic moiety-S-C(O)-steroid or steroid-S-C(O)-organic moiety. The organic moiety is as described above for esters.

"Amide" means an organic moiety as described for ester that comprises 1, 2, 3, 4 or more -C(O)-NR^{PR}- moieties, usually 1 or 2, where R^{PR} is -H or a

protecting group, R^{PR} is usually H. In some embodiments, the $-C(O)NR^{PR}-$ group is linked to the steroid nucleus at R^1-R^6 , R^{10} , R^{15} , R^{17} or R^{18} , i.e., organic moiety- $C(O)NR^{PR}$ -steroid or steroid- $C(O)NR^{PR}$ -organic moiety.

"Ether" means an organic moiety as described for ester that comprises 1, 2, 3, 4 or more $-O-$ moieties, usually 1 or 2. In some embodiments, the $-O-$ group is linked to the steroid nucleus at R^1-R^6 , R^{10} , R^{15} , R^{17} or R^{18} , e.g., organic moiety-O-steroid.

"Thioether" means an organic moiety as described for ester that comprises 1, 2, 3, 4 or more $-S-$ moieties, usually 1 or 2. In some embodiments, the $-S-$ group is linked to the steroid nucleus at R^1-R^6 , R^{10} , R^{15} , R^{17} or R^{18} , e.g., organic moiety-S-steroid.

"Acyl group" means an organic moiety as described for ester that comprises 1, 2, 3, 4 or more $-C(O)-$ groups. In some embodiments, the $-C(O)-$ group is linked to the steroid nucleus at R^1-R^6 , R^{10} , R^{15} , R^{17} or R^{18} , e.g., organic moiety- $C(O)$ -steroid.

"Thioacyl" means an organic moiety as described for ester that comprises 1, 2, 3, 4 or more $-C(S)-$ groups. In some embodiments, the $-C(S)-$ group is linked to the steroid nucleus at R^1-R^6 , R^{10} , R^{15} , R^{17} or R^{18} , e.g., organic moiety- $C(S)$ -steroid.

"Carbonate" means an organic moiety as described for ester that comprises 1, 2, 3, 4 or more $-O-C(O)-O-$ structures. Typically, carbonate groups as used here comprise an organic moiety containing about 1-50 carbon atoms and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si) linked to a formula 1 steroid nucleus at R^1-R^6 , R^{10} , R^{15} , R^{17} or R^{18} through the $-O-C(O)-O-$ structure, e.g., organic moiety- $O-C(O)-O$ -steroid.

"Carbamate" means an organic moiety as described for ester that comprises 1, 2, 3, 4 or more $-O-C(O)NR^{PR}-$ structures where R^{PR} is -H, a protecting group or an organic moiety as described for ester. Typically, carbamate groups as used here comprise an organic moiety containing about 1-50 carbon atoms and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si) linked to a formula 1 steroid nucleus at R^1-R^6 , R^{10} , R^{15} , R^{17} or R^{18} through the $-O-C(O)-$

NR^{PR}- structure, e.g., organic moiety-O-C(O)-NR^{PR}-steroid or steroid-O-C(O)-NR^{PR}-organic moiety.

As used herein, "monosaccharide" means a polyhydroxy aldehyde or ketone having the empirical formula (CH₂O)_n where n is 3, 4, 5, 6 or 7.

Monosaccharide includes open chain and closed chain forms, but will usually be closed chain forms. Monosaccharide includes hexofuranose and pentofuranose sugars such as 2'-deoxyribose, ribose, arabinose, xylose, their 2'-deoxy and 3'-deoxy derivatives and their 2',3'-dideoxy derivatives. Monosaccharide also includes the 2',3' dideoxydidehydro derivative of ribose. Monosaccharides include the D-, L- and DL-isomers of glucose, fructose, mannose, idose, galactose, allose, gulose, altrose, talose, fucose, erythrose, threose, lyxose, erythrulose, ribulose, xylulose, ribose, arabinose, xylose, psicose, sorbose, tagatose, glyceraldehyde, dihydroxyacetone and their monodeoxy derivatives such as rhamnose. Monosaccharides are optionally protected or partially protected.

Optionally substituted moieties such as an optionally substituted alkyl group, an optionally substituted aryl moiety or an optionally substituted heterocycle mean substitutions that include C₁₋₂₀ alkyl moieties, C₂₋₂₀ alkenyl moieties, C₂₋₂₀ alkynyl moieties, aryl moieties, C₂₋₉ heterocycles or substituted derivatives of any of these. Typical substitutions for these organic groups include 1, 2, 3, 4 or more, usually 1 or 2, -O-, -S-, -NR^{PR}-, -C(O)-, -N(R^{PR})₂-, -C(O)OR^{PR}-, -OC(O)R^{PR}-, -OR^{PR}-, -SR^{PR}-, -NO₂-, -CN-, -NHC(O)-, -C(O)NH-, -OC(O)-, -C(O)O-, -O-A8, -S-A8, -C(O)-A8, -OC(O)-A8, -C(O)O-A8, =N-, -N=, -OPO₂R^{PR}-, -OSO₃H or halogen moieties or atoms, where R^{PR} independently is -H, a protecting group or both R^{PR} together are a protecting group and A8 is C₁₋₈ alkyl, C₁₋₄ alkyl-aryl (e.g., benzyl), aryl (e.g. phenyl) or C₁₋₄ alkyl-C₁₋₅ heterocycle. Substitutions are always independently chosen. The organic moieties as described here, and for other any other moieties described herein, exclude obviously unstable moieties, e.g., -O-O-, except where such unstable moieties are transient species that one can use to make a compound with sufficient chemical stability for the one or more of the uses described herein.

Optionally substituted "monosaccharide" comprise any C3-C7 sugar, D-, L- or DL-configurations, e.g., erythrose, glycerol, ribose, deoxyribose, arabinose, glucose, mannose, galactose, fucose, mannose, glucosamine, N-acetylneuraminic acid, N-acetylglucosamine, N-acetylgalactosamine that is optionally substituted at one or more hydroxyl groups. Suitable substitutions include hydrogen, protected hydroxyl, carboxyl, azido, cyano, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -O-C₂₋₆ alkenyl, -S-C₂₋₆ alkenyl, optionally protected amine, optionally protected carboxyl, halogen, thiol or protected thiol. The linkage between the monosaccharide the steroid is α or β .

Optionally substituted "oligosaccharide" comprises two, three, four or more of any C3-C7 sugars that are covalently linked to each other. The linked sugars may have D-, L- or DL-configurations. Suitable sugars and substitutions are as described for monosaccharides. The linkage between the oligosaccharide and the steroid is α or β , as are the linkages between the monosaccharides that comprise the oligosaccharide.

PEG means an ethylene glycol polymer that contains about 20 to about 2000000 linked monomers, typically about 50-1000 linked monomers, usually about 100-300. Polyethylene glycols include PEGs containing various numbers of linked monomers, e.g., PEG20, PEG30, PEG40, PEG60, PEG80, PEG100, PEG115, PEG 200, PEG 300, PEG400, PEG500, PEG600, PEG 1000, PEG1500, PEG2000, PEG 3350, PEG4000, PEG4600, PEG5000, PEG6000, PEG8000, PEG11000, PEG12000, PEG2000000 and any mixtures thereof.

As used herein, position numbers that are given for the formula 1 compounds use the numbering convention for cholesterol.

"Amino acid" means an amino acid moiety that comprises any naturally-occurring or synthetic amino acid residue, i.e., any moiety comprising at least one carboxyl and at least one amino residue directly linked by one, two, three, four, five, six or more carbon atoms, typically one (α) carbon atom. The nature and identity of the intervening structure located between the carboxyl and amino groups can have a variety of structures including those described herein. Typically, amino acids linked to the steroid through the amine group have

sufficient conformation and length to be capable of autocatalytic hydrolysis of the amino acid-steroid bond and release of the steroid. This can occur when the free carboxyl is generated *in vivo* by deesterification, deamidation or peptidolytic cleavage of the precursor containing a linkage between the amino acid's amine group and the steroid. Hydrolysis of the bond between an amino acid's carboxyl or amino group and the steroid can also occur by chemical or enzymatic activity, e.g., esterase cleavage or non-enzymatic hydrolysis.

In general, the amino acids corresponding to the residues employed in the invention compounds are naturally occurring and have no significant pharmacological activity *per se*. However, optimal pharmacokinetic activity, (substantially complete hydrolysis upon hydrolysis of the distal amide or ester bond) may be achieved by using non-naturally occurring amino acid residues. The intervening structure may be as simple as methylene when the amino acid residue is glycyl, or substituted methylene for other α amino acids. The structure ordinarily contains up to about 5 carbon or heteroatoms in the direct linkage between the amino acid's carboxyl carbon and the amine nitrogen. Thus, amino acids can comprise intervening ethylene, propylene, butylene, or pentylene groups or their substituted analogs, such as for example, oxyesters or ethers in which oxygen replaces carbon and, as appropriate, hydrogen. An example of such an intervening structure would be $-\text{CH}-\text{O}-\text{C}(\text{R}^{22})(\text{R}^{23})-$, where R^{22} and R^{23} are independently selected hydrogen or organic moieties as described above for esters. In some embodiments one of R^{22} and R^{23} is hydrogen and the other is a C2-20 organic moiety. Typically the organic moieties contain about 1-20 carbon atoms and 0, 1, 2, 3, 4 or 5 independently selected heteroatoms, which are typically selected from oxygen, nitrogen, sulfur and phosphorus. In general, fewer intervening atoms are used when more rapid hydrolysis is desired, although larger structures are suitable if, e.g., they possess sufficient flexibility or have conformations to allow positioning of the carboxyl group in proximity to the amino acid-steroid bond.

Ordinarily, R^{22} is $-\text{H}$, methyl or hydroxymethyl, usually $-\text{H}$, and R^{23} is a side chain or group of a naturally occurring amino acid. Amino acid side chains

include analogs where the side chain is a C₁₋₁₅ homolog of the corresponding natural compound, e.g., methylene, ethylene, propylene, butylene or a substituted derivative thereof, e.g., an alkyl, ether or alkoxy (e.g., methoxy, ethoxy, propoxy) substituted derivative. In general, for carboxyl-containing side chains, if the C atom of the side chain carboxyl is linked by 5 or less atoms to the N then the carboxyl optionally will be blocked, e.g. by esterification or amidation wherein the ester or amide bonds are hydrolyzable *in vivo*. R²² also is taken together with R³⁰ to form a proline residue (-CH₂-)₃. Thus, R²³ is generally a side group such as -H, -CH₃, -CH(CH₃)₂, -CH₂-CH(CH₃)₂, -CHCH₃-CH₂-CH₃, -CH₂-C₆H₅, -CH₂CH₂-S-CH₃, -CH₂OH, -CH(OH)-CH₃, -CH₂-SH, -CH₂-C₆H₄OH, -CH₂-CO-NH₂, -CH₂-CH₂-CO-NH₂, -CH₂-COOH, -CH₂-CH₂-COOH, -(CH₂)₄-NH₂ and -(CH₂)₃-NH-C(NH₂)-NH₂. R²³ also includes 1-guanidinoprop-3-yl, benzyl, 4-hydroxybenzyl, imidazol-4-yl, indol-3-yl, methoxyphenyl and ethoxyphenyl. The optimal R³⁰ group is readily selected using routine assays.

In general, the amino acid residue has the structure shown in the formulas below. Ordinarily, n is 1 or 2, R²² is -H and R²³ is a moiety containing one or more of the following groups: amino, carboxyl, amide, carboxyl ester, hydroxyl, C₆-C₇ aryl, ether (-O-), thioether (-S-), n-, s- or t-alkyl (C₁ - C₆), guanidiny, imidazolyl, indolyl, sulfhydryl, sulfoxide, and phosphoryl. The R²² and R²³ substituents can have a wide variety of structures including those disclosed herein, e.g., esters, ethers or carbonates.

When the amino acid residues contain one or more chiral centers, any of the D, L, meso, threo or erythro (as appropriate) racemates or mixtures thereof, fall within the scope of this invention. In general, if it is desired to rely on non-enzymatic means of hydrolysis, D isomers should be used. On the other hand, L isomers may be more versatile since they can be susceptible to both non-enzymatic as well as potential targeted enzymatic hydrolysis, and are more efficiently transported by amino acid or dipeptidyl transport systems in the gastrointestinal tract.

Examples of suitable amino acid residues include the following: Glycyl; aminopolycarboxylic acids, e.g., aspartic acid, β -hydroxyaspartic acid, glutamic acid, β -hydroxyglutamic acid, β -methylasspartic acid, β -methylglutamic acid, β,β -dimethylasspartic acid, γ -hydroxyglutamic acid, β,γ -dihydroxyglutamic acid, β -phenylglutamic acid, γ -methyleneglutamic acid, 3-aminoadipic acid, 2-aminopimelic acid, 2-aminosuberic acid and 2-aminosebacic acid residues; amino acid amides such as glutamyl and asparagyl; polyamino- or polybasic-monocarboxylic acids such as arginine, lysine, β -aminoalanine, γ -aminobutyrate, ornithine, citrulline, homoarginine, homocitrulline, 5-hydroxy-2,6-diaminohexanoic acid (commonly, hydroxylysine, including allohydroxylysine) and diaminobutyric acid residues; other basic amino acid residues such as histidyl; diaminodicarboxylic acids such as α,α' -diaminosuccinic acid, α,α' -diaminoglutaric acid, α,α' -diaminoadipic acid, α,α' -diaminopimelic acid, α,α' -diamino- β -hydroxypimelic acid, α,α' -diaminosuberic acid, α,α' -diaminoazelaic acid, and α,α' -diaminosebacic acid residues; imino acids such as proline, 4- or 3-hydroxy-2-pyrrolidinecarboxylic acid (commonly, hydroxyproline, including allohydroxyproline), γ -methylproline, pipercolic acid, 5-hydroxypipercolic acid, $-N[(CH_2)_nCOOR^{PR}]_2$, wherein n is 1, 2, 3, 4, 5 or 6 and R^{PR} is $-H$ or a protecting group, and azetidine-2-carboxylic acid residues; a mono- or di-alkyl (typically $C_1 - C_8$ branched or normal) amino acid such as alanine, valine, leucine, allylglycine, butyrate, norvaline, norleucine, heptyline, α -methylserine, α -amino- α -methyl- γ -hydroxyvaleric acid, α -amino- α -methyl- δ -hydroxyvaleric acid, α -amino- α -methyl- ϵ -hydroxycaproic acid, isovaline, α -methylglutamic acid, α -aminoisobutyric acid, α -aminodiethylacetic acid, α -aminodiisopropylacetic acid, α -aminodi- n -propylacetic acid, α -aminodiisobutylacetic acid, α -aminodi- n -butylacetic acid, α -aminoethylisopropylacetic acid, α -amino- n -propylacetic acid, α -aminodiisoamylacetic acid, α -methylasspartic acid, α -methylglutamic acid, 1-aminocyclopropane-1-carboxylic acid; isoleucine, alloisoleucine, tert-leucine, β -methyltryptophan and α -amino- β -ethyl- β -phenylpropionic acid residues; β -phenylserinyl; aliphatic α -amino- β -hydroxy acids such as serine, β -

hydroxyleucine, β -hydroxynorleucine, β -hydroxynorvaline, and α -amino- β -hydroxystearic acid residues; α -Amino, α -, γ -, δ - or ϵ -hydroxy acids such as homoserine, γ -hydroxynorvaline, δ -hydroxynorvaline and epsilon-hydroxynorleucine residues; canavinyl and canalinyl; γ -hydroxyornithinyl; 2-Hexosaminic acids such as D-glucosaminic acid or D-galactosaminic acid residues; α -amino- β -thiols such as penicillamine, β -thiolnorvaline or β -thiolbutyrine residues; other sulfur containing amino acid residues including cysteine; homocystine; β -phenylmethionine; methionine; S-allyl-L-cysteine sulfoxide; 2-thiolhistidine; cystathionine; and thiol ethers of cysteine or homocysteine; phenylalanine, tryptophan and ring-substituted α amino acids such as the phenyl- or cyclohexylamino acids α -aminophenylacetic acid, α -aminocyclohexylacetic acid and α -amino- β -cyclohexylpropionic acid; phenylalanine analogues and derivatives comprising aryl, lower alkyl, hydroxy, guanidino, oxyalkylether, nitro, sulfur or halo-substituted phenyl (e.g., tyrosine, methyltyrosine and o-chloro-, p-chloro-, 3,4-dicloro, o-, m- or p-methyl-, 2,4,6-trimethyl-, 2-ethoxy-5-nitro, 2-hydroxy-5-nitro and p-nitro-phenylalanine); furyl-, thienyl-, pyridyl-, pyrimidinyl-, purine or naphthylalanines; and tryptophan analogues and derivatives including kynurenine, 3-hydroxykynurenine, 2-hydroxytryptophan and 4-carboxytryptophan residues; α -amino substituted amino acid residues including sarcosine (N-methylglycine), N-benzylglycine, N-methylalanine, N-benzylalanine, N-methylphenylalanine, N-benzylphenylalanine, N-methylvaline and N-benzylvaline; and α -Hydroxy and substituted α -hydroxy amino acid residues including serine, threonine, allothreonine, phosphoserine and phosphothreonine residues.

Any one of the foregoing or other known amino acids are suitably employed in this invention. Typically amino acids are capable of autocatalytically hydrolyzing the amino acid-steroid bond. Thus, they typically contain, or upon being hydrolyzed *in vivo*, contain a free carboxyl group or amine group.

Also of interest are hydrophobic amino acids such as mono-or di-alkyl or aryl amino acids, cycloalkylamino acids and the like. These residues, together

with R²⁹- R³⁴ (R³¹-R³⁴ are defined below) can contribute to cell permeability by modulating the lipophilicity of a formula 1 or formula 2 compound. Typically, the residue does not contain a sulfhydryl or guanidino substituent.

Peptide. One, 2, 3 or more of R¹-R⁴ can comprise a "peptide", i.e., two or more amino acids as defined above. Typically the amino acids are linked through normal peptide bonds, i.e., -CO-NH-, between adjacent amino acid residues. Peptides comprise dipeptides (dimers), tripeptides (trimers), short peptides of 4, 5, 6, 8, 10 or 15 residues, and longer peptides or proteins having about 100 or more residues. Invention compounds that comprise a peptide can be used as immunogens, prodrugs or as synthetic precursors for other steroid derivatives. In one embodiment, the peptide will contain a peptidolytic enzyme cleavage site at the peptide bond linking the first residue and the next residue distal to the steroid residue. Such cleavage sites are optionally flanked by enzymatic recognition structures, e.g. particular residues recognized by a hydrolytic enzyme, e.g., a peptidase located in the serum or in cells.

Peptidolytic enzymes are well known, and in particular include carboxypeptidases. Carboxypeptidases digest polypeptides by removing C-terminal residues, and are specific in many instances for particular C-terminal sequences. Such enzymes and their substrate requirements in general are well known. For example, a dipeptide having a given pair of residues and a free carboxyl terminus is covalently bonded through its α -amino group to the steroid nucleus. It is expected that the peptide will be cleaved by the appropriate dipeptidase, protease or by chemical hydrolysis, leaving the carboxyl of the proximal amino acid residue to autocatalytically cleave the amide bond.

Examples of suitable dipeptidyl groups (designated by their single letter symbols) are shown in the table below.

SYMBOL		
1-Letter	3-Letter	AMINO ACID
Y	Tyr	tyrosine
G	Gly	glycine
F	Phe	phenylalanine
M	Met	methionine

A	Ala	alanine
S	Ser	serine
I	Ile	isoleucine
L	Leu	leucine
T	Thr	threonine
V	Val	valine
P	Pro	proline
K	Lys	lysine
H	His	histidine
Q	Gln	glutamine
E	Glu	glutamic acid
W	Trp	tryptophan
R	Arg	arginine
D	Asp	aspartic acid
N	Asn	asparagine
C	Cys	cysteine

Dipeptides

AA, AR, AN, AD, AC, AE, AQ, AG, AH, AI, AL, AK, AM, AF, AP, AS, AT, AW, AY, AV, RA, RR, RN, RD, RC, RE, RQ, RG, RH, RI, RL, RK, RM, RF, RP, RS, RT, RW, RY, RV, NA, NR, NN, ND, NC, NE, NQ, NG, NH, NI, NL, NK, NM, NF, NP, NS, NT, NW, NY, NV, DA, DR, DN, DD, DC, DE, DQ, DG, DH, DI, DL, DK, DM, DF, DP, DS, DT, DW, DY, DV, CA, CR, CN, CD, CC, CE, CQ, CG, CH, CI, CL, CK, CM, CF, CP, CS, CT, CW, CY, CV, EA, ER, EN, ED, EC, EE, EQ, EG, EH, EI, EL, EK, EM, EF, EP, ES, ET, EW, EY, EV, QA, QR, QN, QD, QC, QE, QQ, QG, QH, QI, QL, QK, QM, QF, QP, QS, QT, QW, QY, QV, GA, GR, GN, GD, GC, GE, GQ, GG, GH, GI, GL, GK, GM, GF, GP, GS, GT, GW, GY, GV, HA, HR, HN, HD, HC, HE, HQ, HG, HH, HI, HL, HK, HM, HF, HP, HS, HT, HW, HY, HV, IA, IR, IN, ID, IC, IE, IQ, IG, IH, II, IL, IK, IM, IF, IP, IS, IT, IW, IY, IV, LA, LR, LN, LD, LC, LE, LQ, LG, LH, LI, LL, LK, LM, LF, LP, LS, LT, LW, LY, LV, KA, KR, KN, KD, KC, KE, KQ, KG, KH, KI, KL, KK, KM, KF, KP, KS, KT, KW, KY, KV, MA, MR, MN, MD, MC, ME, MQ, MG, MH, MI, ML, MK, MM, MF, MP, MS, MT, MW, MY, MV, FA, FR, FN, FD, FC, FE, FQ, FG, FH, FI, FL, FK, FM, FF, FP, FS, FT, FW, FY, FV, PA, PR, PN, PD, PC, PE, PQ, PG, PH, PI, PL, PK, PM, PF, PP, PS, PT, PW, PY, PV, SA, SR, SN, SD, SC, SE, SQ, SG, SH, SI, SL, SK, SM, SF, SP, SS, ST, SW, SY, SV, TA, TR, TN, TD, TC, TE, TQ, TG, TH, TI, TL, TK, TM, TF, TP, TS, TT, TW, TY, TV, WA, WR, WN, WD, WC, WE, WQ, WG, WH, WI, WL, WK, WM, WF, WP, WS, WT, WW, WY, WV, YA, YR, YN, YD, YC, YE, YQ, YG, YH, YI, YL, YK, YM, YF, YP, YS, YT, YW, YY, YV, VA, VR, VN, VD, VC, VE, VQ, VG, VH, VI, VL, VK, VM, VF, VP, VS, VT, VW, VY, VV

Such dipeptides include species where both amino acids are in the L configuration, the D configuration or mixtures of configurations.

Tripeptides, i.e., 3 linked amino acid residues, are also useful embodiments. Tripeptides include those where A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W or Y is linked by a standard peptide bond to the amino or the carboxyl terminus of any of the dipeptides listed above. The sequence –X1-pro-

X2- (where X1 is any amino acid and X2 is hydrogen, any amino acid residue or a carboxyl ester of proline) will be cleaved by luminal carboxypeptidase to yield X1 with a free carboxyl, which in turn autocatalytically cleaves the amide bond. X2 usually will be a benzyl ester of the carboxy group of X2. Other embodiments include tetrapeptides such as ones where any two of the dipeptides listed above, which may be the same or different dipeptides (e.g., AA and AA linked together or, e.g., AA and GI linked together), are linked to each other by a peptide bond through the amino terminus or carboxyl terminus. One, 2 or more tetrapeptides may be bonded to the formula 1 or formula 2 compound through the tetrapeptide's amino or carboxyl terminus.

In some embodiments, the formula 1 or formula 2 compound comprises one or more amino acids or peptides having the structure (A), (B) or (C):
 (A) $R^{32}-NH-[C(R^{29})(R^{30})]_b-C(O)-N(R^{31})-[C(R^{29})(R^{30})]_a-C(O)-O\text{-steroid}$,
 (B) $R^{33}-O-[C(O)-[C(R^{29})(R^{30})]_d-N(R^{31})]_g-C(O)-[C(R^{29})(R^{30})]_c-N(R^{31})-O\text{-steroid}$, or
 (C) $R^{33}-O-[C(O)-[C(R^{29})(R^{30})]_d-N(R^{31})]_e-C(O)-[C(R^{29})(R^{30})]_c-N(R^{31})-C(O)-O\text{-steroid}$, wherein (A), (B) or (C) are independently selected and they are bonded to 1, 2, 3 or more of R^1 through R^4 , where each $R^{29}-R^{31}$ is independently selected; R^{29} independently are -H or a C1-20 organic moiety (e.g., C_{1-6} alkyl, e.g. $-CH_3$ or $-C_2H_5$); R^{30} independently are the side chain of an amino acid, including the side chain of naturally occurring amino acids as described above, e.g., -H, $-CH_3$, $-CH_2C_6H_5$; R^{31} is -H or a protecting group; R^{32} and R^{33} independently comprise -H, a protecting group, an ester or an amide where each atom or group is independently chosen; a, b, c and d independently are 1, 2, 3, 4 or 5, usually 1; e, f and g independently are an integer from 0 to about 1000, typically they independently are 0, 1, 2, 3, 4, 5, 6, 7 or 8; a, b, c and d independently are 1 or 2; e, f and g independently are 0, 1, 2, 3, 4 or 5.

If the amino acid(s) or residue(s) has 2 or more amine groups, e.g., a lysinyl or arginyl, or ornithinyl residue, then R^{29} is usually -H and R^{30} may comprise $-[C(R^{34})]_{n2}N(R^{PR})-$ where $n2$ is 0, 1, 2, 3, 4, 5 or 6, R^{PR} is -H or a protecting group and each R^{34} independently is -H, C_1-C_{20} optionally substituted

alkyl, C₆-C₂₀ optionally substituted aryl, C₇-C₂₀ optionally substituted alkylaryl, C₇-C₂₀ optionally substituted arylalkyl, C₁-C₂₀ optionally substituted alkoxy, C₆-C₂₀ optionally substituted aryloxy or hydroxyl. Such compounds will contain a plurality of steroid moieties. For example when both the epsilon (ϵ) or delta (δ) and alpha (α) amino groups of lysine or ornithine are substituted with steroid moieties the amidate is believed to be capable of releasing two molecules of active drug, each expected to emerge under different pharmacokinetics and therefore further sustaining the drug release.

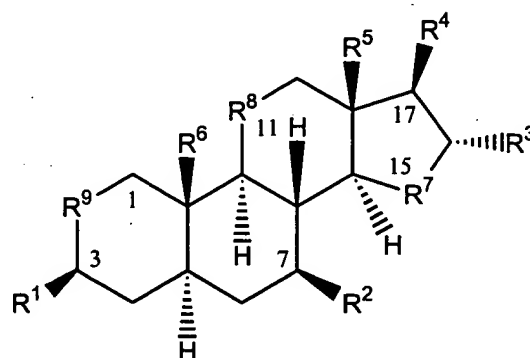
List of cancers

Treatments include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, non-small cell lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, retinoblastoma and any precancerous lesion or precancerous tissue of any of these malignancies.

Embodiments

Exemplary embodiments of species and genera of formula 1 compounds are named as described below.

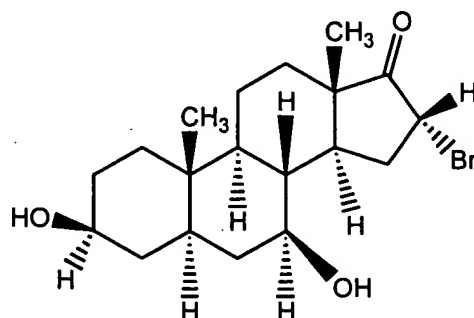
Group 1. Exemplary embodiments include the use of the formula 2 compounds named according to the compound structure designations given in Tables A and B below. Each compound named in Table B is depicted as a compound having formula B



B

where R^5 and R^6 are both $-CH_3$, there is no double bond at the 1-2-, 4-5- or 5-6-positions, one R^4 is hydrogen, R^7 , R^8 and R^9 are all $-CH_2-$ and R^1 , R^2 , R^3 and R^4 are the substituents designated in Table A. The compounds named according to Tables A and B are referred to as "group 1" compounds.

Compounds named in Table B are named by numbers assigned to R^1 , R^2 , R^3 and R^4 according to the following compound naming convention, $R^1.R^2.R^3.R^4$, based on the numbered chemical substituents depicted in Table A. Each Table A number specifies a different structure for each of R^1 , R^2 , R^3 and R^4 . When R^1 , R^2 , R^3 or R^4 is a divalent moiety, e.g., $=O$, the hydrogen at the corresponding position is absent. Thus, the group 1 compound named 1.2.1.1 is a formula B structure with a β -hydroxyl bonded to carbons at the 3- and 7-positions (the variable groups R^1 and R^2 respectively), an α -bromine bonded to carbon 16 (the variable group R^3) and double bonded oxygen ($=O$) at carbon 17 (the variable group R^4), i.e., 1.2.1.1 has the structure shown below.



1.2.1.1

TABLE A

R ¹	R ²
1 -OH	1 -H
2 =O	2 -OH
3 -SH	3 =O
4 =S	4 -CH ₃
5 -O-CH ₃	5 -OCH ₃
6 -O-S(O)(O)-O ⁻ Na ⁺	6 -OC ₂ H ₅
7 -O-S(O)(O)-OC ₂ H ₅	7 -OCH ₂ CH ₂ CH ₃
8 -CH ₃	8 -OCH ₂ CH ₂ CH ₂ CH ₃
9 -H	9 -Cl
10 -OC(O)C(CH ₃) ₃	10 -Br

R ³	R ⁴
1 -Br	1 =O
2 -Cl	2 -OH
3 -I	3 -H
4 -F	4 -F
5 -H	5 -Cl
6 -OH	6 -Br
7 =O	7 -I
8 -O-C(O)-CH ₃	8 -O-C(O)-CH ₃
9 -O-C(O)-CH ₂ CH ₃	9 -O-C(O)-CH ₂ CH ₃
10 -O-C(O)-CH ₂ CH ₂ CH ₃	10 -O-C(O)-CH ₂ CH ₂ CH ₃

TABLE B

1.1.1.1, 1.1.1.2, 1.1.1.3, 1.1.1.4, 1.1.1.5, 1.1.1.6, 1.1.1.7, 1.1.1.8, 1.1.1.9, 1.1.1.10, 1.1.2.1, 1.1.2.2, 1.1.2.3, 1.1.2.4, 1.1.2.5, 1.1.2.6, 1.1.2.7, 1.1.2.8, 1.1.2.9, 1.1.2.10, 1.1.3.1, 1.1.3.2, 1.1.3.3, 1.1.3.4, 1.1.3.5, 1.1.3.6, 1.1.3.7, 1.1.3.8, 1.1.3.9, 1.1.3.10, 1.1.4.1, 1.1.4.2, 1.1.4.3, 1.1.4.4, 1.1.4.5, 1.1.4.6, 1.1.4.7, 1.1.4.8, 1.1.4.9, 1.1.4.10, 1.1.5.1, 1.1.5.2, 1.1.5.3, 1.1.5.4, 1.1.5.5, 1.1.5.6, 1.1.5.7, 1.1.5.8, 1.1.5.9, 1.1.5.10, 1.1.6.1, 1.1.6.2, 1.1.6.3, 1.1.6.4, 1.1.6.5, 1.1.6.6, 1.1.6.7, 1.1.6.8, 1.1.6.9, 1.1.6.10, 1.1.7.1, 1.1.7.2, 1.1.7.3, 1.1.7.4, 1.1.7.5, 1.1.7.6, 1.1.7.7, 1.1.7.8, 1.1.7.9, 1.1.7.10, 1.1.8.1, 1.1.8.2, 1.1.8.3, 1.1.8.4, 1.1.8.5, 1.1.8.6, 1.1.8.7, 1.1.8.8, 1.1.8.9, 1.1.8.10, 1.1.9.1, 1.1.9.2, 1.1.9.3, 1.1.9.4, 1.1.9.5, 1.1.9.6, 1.1.9.7, 1.1.9.8, 1.1.9.9, 1.1.9.10, 1.1.10.1, 1.1.10.2, 1.1.10.3, 1.1.10.4, 1.1.10.5, 1.1.10.6, 1.1.10.7, 1.1.10.8, 1.1.10.9, 1.1.10.10, 1.2.1.1, 1.2.1.2, 1.2.1.3, 1.2.1.4, 1.2.1.5, 1.2.1.6, 1.2.1.7, 1.2.1.8, 1.2.1.9, 1.2.1.10, 1.2.2.1, 1.2.2.2, 1.2.2.3, 1.2.2.4, 1.2.2.5, 1.2.2.6, 1.2.2.7, 1.2.2.8, 1.2.2.9, 1.2.2.10, 1.2.3.1, 1.2.3.2, 1.2.3.3, 1.2.3.4, 1.2.3.5, 1.2.3.6, 1.2.3.7, 1.2.3.8, 1.2.3.9, 1.2.3.10, 1.2.4.1, 1.2.4.2, 1.2.4.3, 1.2.4.4, 1.2.4.5, 1.2.4.6, 1.2.4.7, 1.2.4.8, 1.2.4.9, 1.2.4.10, 1.2.5.1, 1.2.5.2, 1.2.5.3, 1.2.5.4, 1.2.5.5, 1.2.5.6, 1.2.5.7, 1.2.5.8, 1.2.5.9, 1.2.5.10, 1.2.6.1, 1.2.6.2, 1.2.6.3, 1.2.6.4, 1.2.6.5, 1.2.6.6, 1.2.6.7, 1.2.6.8, 1.2.6.9, 1.2.6.10, 1.2.7.1, 1.2.7.2, 1.2.7.3, 1.2.7.4, 1.2.7.5, 1.2.7.6, 1.2.7.7, 1.2.7.8, 1.2.7.9, 1.2.7.10, 1.2.8.1, 1.2.8.2, 1.2.8.3, 1.2.8.4, 1.2.8.5, 1.2.8.6, 1.2.8.7, 1.2.8.8, 1.2.8.9, 1.2.8.10, 1.2.9.1, 1.2.9.2, 1.2.9.3, 1.2.9.4, 1.2.9.5, 1.2.9.6, 1.2.9.7, 1.2.9.8, 1.2.9.9, 1.2.9.10, 1.2.10.1, 1.2.10.2, 1.2.10.3, 1.2.10.4, 1.2.10.5, 1.2.10.6, 1.2.10.7, 1.2.10.8, 1.2.10.9, 1.2.10.10, 1.3.1.1, 1.3.1.2, 1.3.1.3, 1.3.1.4, 1.3.1.5, 1.3.1.6, 1.3.1.7, 1.3.1.8, 1.3.1.9, 1.3.1.10, 1.3.2.1, 1.3.2.2, 1.3.2.3, 1.3.2.4, 1.3.2.5, 1.3.2.6, 1.3.2.7, 1.3.2.8, 1.3.2.9, 1.3.2.10, 1.3.3.1, 1.3.3.2, 1.3.3.3, 1.3.3.4, 1.3.3.5, 1.3.3.6, 1.3.3.7, 1.3.3.8, 1.3.3.9, 1.3.3.10, 1.3.4.1, 1.3.4.2, 1.3.4.3, 1.3.4.4, 1.3.4.5, 1.3.4.6, 1.3.4.7, 1.3.4.8, 1.3.4.9, 1.3.4.10, 1.3.5.1, 1.3.5.2, 1.3.5.3, 1.3.5.4, 1.3.5.5, 1.3.5.6, 1.3.5.7, 1.3.5.8, 1.3.5.9, 1.3.5.10, 1.3.6.1, 1.3.6.2, 1.3.6.3, 1.3.6.4, 1.3.6.5, 1.3.6.6, 1.3.6.7, 1.3.6.8, 1.3.6.9, 1.3.6.10, 1.3.7.1, 1.3.7.2, 1.3.7.3, 1.3.7.4, 1.3.7.5, 1.3.7.6, 1.3.7.7, 1.3.7.8, 1.3.7.9, 1.3.7.10, 1.3.8.1, 1.3.8.2, 1.3.8.3, 1.3.8.4, 1.3.8.5, 1.3.8.6, 1.3.8.7, 1.3.8.8, 1.3.8.9, 1.3.8.10, 1.3.9.1, 1.3.9.2, 1.3.9.3, 1.3.9.4, 1.3.9.5, 1.3.9.6, 1.3.9.7, 1.3.9.8, 1.3.9.9, 1.3.9.10, 1.3.10.1, 1.3.10.2,

[illegible]

1.10.9.9, 1.10.9.10, 1.10.10.1, 1.10.10.2, 1.10.10.3, 1.10.10.4, 1.10.10.5, 1.10.10.6, 1.10.10.7, 1.10.10.8,
1.10.10.9, 1.10.10.10, 2.1.1.1, 2.1.1.2, 2.1.1.3, 2.1.1.4, 2.1.1.5, 2.1.1.6, 2.1.1.7, 2.1.1.8, 2.1.1.9, 2.1.1.10,
2.1.2.1, 2.1.2.2, 2.1.2.3, 2.1.2.4, 2.1.2.5, 2.1.2.6, 2.1.2.7, 2.1.2.8, 2.1.2.9, 2.1.2.10, 2.1.3.1, 2.1.3.2, 2.1.3.3,
2.1.3.4, 2.1.3.5, 2.1.3.6, 2.1.3.7, 2.1.3.8, 2.1.3.9, 2.1.3.10, 2.1.4.1, 2.1.4.2, 2.1.4.3, 2.1.4.4, 2.1.4.5, 2.1.4.6,
2.1.4.7, 2.1.4.8, 2.1.4.9, 2.1.4.10, 2.1.5.1, 2.1.5.2, 2.1.5.3, 2.1.5.4, 2.1.5.5, 2.1.5.6, 2.1.5.7, 2.1.5.8, 2.1.5.9,
2.1.5.10, 2.1.6.1, 2.1.6.2, 2.1.6.3, 2.1.6.4, 2.1.6.5, 2.1.6.6, 2.1.6.7, 2.1.6.8, 2.1.6.9, 2.1.6.10, 2.1.7.1, 2.1.7.2,
2.1.7.3, 2.1.7.4, 2.1.7.5, 2.1.7.6, 2.1.7.7, 2.1.7.8, 2.1.7.9, 2.1.7.10, 2.1.8.1, 2.1.8.2, 2.1.8.3, 2.1.8.4, 2.1.8.5,
2.1.8.6, 2.1.8.7, 2.1.8.8, 2.1.8.9, 2.1.8.10, 2.1.9.1, 2.1.9.2, 2.1.9.3, 2.1.9.4, 2.1.9.5, 2.1.9.6, 2.1.9.7, 2.1.9.8,
2.1.9.9, 2.1.9.10, 2.1.10.1, 2.1.10.2, 2.1.10.3, 2.1.10.4, 2.1.10.5, 2.1.10.6, 2.1.10.7, 2.1.10.8, 2.1.10.9,
2.1.10.10, 2.2.1.1, 2.2.1.2, 2.2.1.3, 2.2.1.4, 2.2.1.5, 2.2.1.6, 2.2.1.7, 2.2.1.8, 2.2.1.9, 2.2.1.10, 2.2.2.1,
2.2.2.2, 2.2.2.3, 2.2.2.4, 2.2.2.5, 2.2.2.6, 2.2.2.7, 2.2.2.8, 2.2.2.9, 2.2.2.10, 2.2.3.1, 2.2.3.2, 2.2.3.3, 2.2.3.4,
2.2.3.5, 2.2.3.6, 2.2.3.7, 2.2.3.8, 2.2.3.9, 2.2.3.10, 2.2.4.1, 2.2.4.2, 2.2.4.3, 2.2.4.4, 2.2.4.5, 2.2.4.6, 2.2.4.7,
2.2.4.8, 2.2.4.9, 2.2.4.10, 2.2.5.1, 2.2.5.2, 2.2.5.3, 2.2.5.4, 2.2.5.5, 2.2.5.6, 2.2.5.7, 2.2.5.8, 2.2.5.9, 2.2.5.10,
2.2.6.1, 2.2.6.2, 2.2.6.3, 2.2.6.4, 2.2.6.5, 2.2.6.6, 2.2.6.7, 2.2.6.8, 2.2.6.9, 2.2.6.10, 2.2.7.1, 2.2.7.2, 2.2.7.3,
2.2.7.4, 2.2.7.5, 2.2.7.6, 2.2.7.7, 2.2.7.8, 2.2.7.9, 2.2.7.10, 2.2.8.1, 2.2.8.2, 2.2.8.3, 2.2.8.4, 2.2.8.5, 2.2.8.6,
2.2.8.7, 2.2.8.8, 2.2.8.9, 2.2.8.10, 2.2.9.1, 2.2.9.2, 2.2.9.3, 2.2.9.4, 2.2.9.5, 2.2.9.6, 2.2.9.7, 2.2.9.8, 2.2.9.9,
2.2.9.10, 2.2.10.1, 2.2.10.2, 2.2.10.3, 2.2.10.4, 2.2.10.5, 2.2.10.6, 2.2.10.7, 2.2.10.8, 2.2.10.9, 2.2.10.10,
2.3.1.1, 2.3.1.2, 2.3.1.3, 2.3.1.4, 2.3.1.5, 2.3.1.6, 2.3.1.7, 2.3.1.8, 2.3.1.9, 2.3.1.10, 2.3.2.1, 2.3.2.2, 2.3.2.3,
2.3.2.4, 2.3.2.5, 2.3.2.6, 2.3.2.7, 2.3.2.8, 2.3.2.9, 2.3.2.10, 2.3.3.1, 2.3.3.2, 2.3.3.3, 2.3.3.4, 2.3.3.5, 2.3.3.6,
2.3.3.7, 2.3.3.8, 2.3.3.9, 2.3.3.10, 2.3.4.1, 2.3.4.2, 2.3.4.3, 2.3.4.4, 2.3.4.5, 2.3.4.6, 2.3.4.7, 2.3.4.8, 2.3.4.9,
2.3.4.10, 2.3.5.1, 2.3.5.2, 2.3.5.3, 2.3.5.4, 2.3.5.5, 2.3.5.6, 2.3.5.7, 2.3.5.8, 2.3.5.9, 2.3.5.10, 2.3.6.1, 2.3.6.2,
2.3.6.3, 2.3.6.4, 2.3.6.5, 2.3.6.6, 2.3.6.7, 2.3.6.8, 2.3.6.9, 2.3.6.10, 2.3.7.1, 2.3.7.2, 2.3.7.3, 2.3.7.4, 2.3.7.5,
2.3.7.6, 2.3.7.7, 2.3.7.8, 2.3.7.9, 2.3.7.10, 2.3.8.1, 2.3.8.2, 2.3.8.3, 2.3.8.4, 2.3.8.5, 2.3.8.6, 2.3.8.7, 2.3.8.8,
2.3.8.9, 2.3.8.10, 2.3.9.1, 2.3.9.2, 2.3.9.3, 2.3.9.4, 2.3.9.5, 2.3.9.6, 2.3.9.7, 2.3.9.8, 2.3.9.9, 2.3.9.10,
2.3.10.1, 2.3.10.2, 2.3.10.3, 2.3.10.4, 2.3.10.5, 2.3.10.6, 2.3.10.7, 2.3.10.8, 2.3.10.9, 2.3.10.10, 2.4.1.1,
2.4.1.2, 2.4.1.3, 2.4.1.4, 2.4.1.5, 2.4.1.6, 2.4.1.7, 2.4.1.8, 2.4.1.9, 2.4.1.10, 2.4.2.1, 2.4.2.2, 2.4.2.3, 2.4.2.4,
2.4.2.5, 2.4.2.6, 2.4.2.7, 2.4.2.8, 2.4.2.9, 2.4.2.10, 2.4.3.1, 2.4.3.2, 2.4.3.3, 2.4.3.4, 2.4.3.5, 2.4.3.6, 2.4.3.7,
2.4.3.8, 2.4.3.9, 2.4.3.10, 2.4.4.1, 2.4.4.2, 2.4.4.3, 2.4.4.4, 2.4.4.5, 2.4.4.6, 2.4.4.7, 2.4.4.8, 2.4.4.9, 2.4.4.10,
2.4.5.1, 2.4.5.2, 2.4.5.3, 2.4.5.4, 2.4.5.5, 2.4.5.6, 2.4.5.7, 2.4.5.8, 2.4.5.9, 2.4.5.10, 2.4.6.1, 2.4.6.2, 2.4.6.3,
2.4.6.4, 2.4.6.5, 2.4.6.6, 2.4.6.7, 2.4.6.8, 2.4.6.9, 2.4.6.10, 2.4.7.1, 2.4.7.2, 2.4.7.3, 2.4.7.4, 2.4.7.5, 2.4.7.6,
2.4.7.7, 2.4.7.8, 2.4.7.9, 2.4.7.10, 2.4.8.1, 2.4.8.2, 2.4.8.3, 2.4.8.4, 2.4.8.5, 2.4.8.6, 2.4.8.7, 2.4.8.8, 2.4.8.9,
2.4.8.10, 2.4.9.1, 2.4.9.2, 2.4.9.3, 2.4.9.4, 2.4.9.5, 2.4.9.6, 2.4.9.7, 2.4.9.8, 2.4.9.9, 2.4.9.10, 2.4.10.1,
2.4.10.2, 2.4.10.3, 2.4.10.4, 2.4.10.5, 2.4.10.6, 2.4.10.7, 2.4.10.8, 2.4.10.9, 2.4.10.10, 2.5.1.1, 2.5.1.2,
2.5.1.3, 2.5.1.4, 2.5.1.5, 2.5.1.6, 2.5.1.7, 2.5.1.8, 2.5.1.9, 2.5.1.10, 2.5.2.1, 2.5.2.2, 2.5.2.3, 2.5.2.4, 2.5.2.5,
2.5.2.6, 2.5.2.7, 2.5.2.8, 2.5.2.9, 2.5.2.10, 2.5.3.1, 2.5.3.2, 2.5.3.3, 2.5.3.4, 2.5.3.5, 2.5.3.6, 2.5.3.7, 2.5.3.8,
2.5.3.9, 2.5.3.10, 2.5.4.1, 2.5.4.2, 2.5.4.3, 2.5.4.4, 2.5.4.5, 2.5.4.6, 2.5.4.7, 2.5.4.8, 2.5.4.9, 2.5.4.10, 2.5.5.1,
2.5.5.2, 2.5.5.3, 2.5.5.4, 2.5.5.5, 2.5.5.6, 2.5.5.7, 2.5.5.8, 2.5.5.9, 2.5.5.10, 2.5.6.1, 2.5.6.2, 2.5.6.3, 2.5.6.4,
2.5.6.5, 2.5.6.6, 2.5.6.7, 2.5.6.8, 2.5.6.9, 2.5.6.10, 2.5.7.1, 2.5.7.2, 2.5.7.3, 2.5.7.4, 2.5.7.5, 2.5.7.6, 2.5.7.7,
2.5.7.8, 2.5.7.9, 2.5.7.10, 2.5.8.1, 2.5.8.2, 2.5.8.3, 2.5.8.4, 2.5.8.5, 2.5.8.6, 2.5.8.7, 2.5.8.8, 2.5.8.9, 2.5.8.10,
2.5.9.1, 2.5.9.2, 2.5.9.3, 2.5.9.4, 2.5.9.5, 2.5.9.6, 2.5.9.7, 2.5.9.8, 2.5.9.9, 2.5.9.10, 2.5.10.1, 2.5.10.2,
2.5.10.3, 2.5.10.4, 2.5.10.5, 2.5.10.6, 2.5.10.7, 2.5.10.8, 2.5.10.9, 2.5.10.10, 2.6.1.1, 2.6.1.2, 2.6.1.3,
2.6.1.4, 2.6.1.5, 2.6.1.6, 2.6.1.7, 2.6.1.8, 2.6.1.9, 2.6.1.10, 2.6.2.1, 2.6.2.2, 2.6.2.3, 2.6.2.4, 2.6.2.5, 2.6.2.6,
2.6.2.7, 2.6.2.8, 2.6.2.9, 2.6.2.10, 2.6.3.1, 2.6.3.2, 2.6.3.3, 2.6.3.4, 2.6.3.5, 2.6.3.6, 2.6.3.7, 2.6.3.8, 2.6.3.9,
2.6.3.10, 2.6.4.1, 2.6.4.2, 2.6.4.3, 2.6.4.4, 2.6.4.5, 2.6.4.6, 2.6.4.7, 2.6.4.8, 2.6.4.9, 2.6.4.10, 2.6.5.1, 2.6.5.2,
2.6.5.3, 2.6.5.4, 2.6.5.5, 2.6.5.6, 2.6.5.7, 2.6.5.8, 2.6.5.9, 2.6.5.10, 2.6.6.1, 2.6.6.2, 2.6.6.3, 2.6.6.4, 2.6.6.5,
2.6.6.6, 2.6.6.7, 2.6.6.8, 2.6.6.9, 2.6.6.10, 2.6.7.1, 2.6.7.2, 2.6.7.3, 2.6.7.4, 2.6.7.5, 2.6.7.6, 2.6.7.7, 2.6.7.8,
2.6.7.9, 2.6.7.10, 2.6.8.1, 2.6.8.2, 2.6.8.3, 2.6.8.4, 2.6.8.5, 2.6.8.6, 2.6.8.7, 2.6.8.8, 2.6.8.9, 2.6.8.10, 2.6.9.1,
2.6.9.2, 2.6.9.3, 2.6.9.4, 2.6.9.5, 2.6.9.6, 2.6.9.7, 2.6.9.8, 2.6.9.9, 2.6.9.10, 2.6.10.1, 2.6.10.2, 2.6.10.3,
2.6.10.4, 2.6.10.5, 2.6.10.6, 2.6.10.7, 2.6.10.8, 2.6.10.9, 2.6.10.10, 2.7.1.1, 2.7.1.2, 2.7.1.3, 2.7.1.4, 2.7.1.5,
2.7.1.6, 2.7.1.7, 2.7.1.8, 2.7.1.9, 2.7.1.10, 2.7.2.1, 2.7.2.2, 2.7.2.3, 2.7.2.4, 2.7.2.5, 2.7.2.6, 2.7.2.7, 2.7.2.8,
2.7.2.9, 2.7.2.10, 2.7.3.1, 2.7.3.2, 2.7.3.3, 2.7.3.4, 2.7.3.5, 2.7.3.6, 2.7.3.7, 2.7.3.8, 2.7.3.9, 2.7.3.10, 2.7.4.1,
2.7.4.2, 2.7.4.3, 2.7.4.4, 2.7.4.5, 2.7.4.6, 2.7.4.7, 2.7.4.8, 2.7.4.9, 2.7.4.10, 2.7.5.1, 2.7.5.2, 2.7.5.3, 2.7.5.4,
2.7.5.5, 2.7.5.6, 2.7.5.7, 2.7.5.8, 2.7.5.9, 2.7.5.10, 2.7.6.1, 2.7.6.2, 2.7.6.3, 2.7.6.4, 2.7.6.5, 2.7.6.6, 2.7.6.7,
2.7.6.8, 2.7.6.9, 2.7.6.10, 2.7.7.1, 2.7.7.2, 2.7.7.3, 2.7.7.4, 2.7.7.5, 2.7.7.6, 2.7.7.7, 2.7.7.8, 2.7.7.9, 2.7.7.10,
2.7.8.1, 2.7.8.2, 2.7.8.3, 2.7.8.4, 2.7.8.5, 2.7.8.6, 2.7.8.7, 2.7.8.8, 2.7.8.9, 2.7.8.10, 2.7.9.1, 2.7.9.2, 2.7.9.3,
2.7.9.4, 2.7.9.5, 2.7.9.6, 2.7.9.7, 2.7.9.8, 2.7.9.9, 2.7.9.10, 2.7.10.1, 2.7.10.2, 2.7.10.3, 2.7.10.4, 2.7.10.5,

2.7.10.6, 2.7.10.7, 2.7.10.8, 2.7.10.9, 2.7.10.10, 2.8.1.1, 2.8.1.2, 2.8.1.3, 2.8.1.4, 2.8.1.5, 2.8.1.6, 2.8.1.7, 2.8.1.8, 2.8.1.9, 2.8.1.10, 2.8.2.1, 2.8.2.2, 2.8.2.3, 2.8.2.4, 2.8.2.5, 2.8.2.6, 2.8.2.7, 2.8.2.8, 2.8.2.9, 2.8.2.10, 2.8.3.1, 2.8.3.2, 2.8.3.3, 2.8.3.4, 2.8.3.5, 2.8.3.6, 2.8.3.7, 2.8.3.8, 2.8.3.9, 2.8.3.10, 2.8.4.1, 2.8.4.2, 2.8.4.3, 2.8.4.4, 2.8.4.5, 2.8.4.6, 2.8.4.7, 2.8.4.8, 2.8.4.9, 2.8.4.10, 2.8.5.1, 2.8.5.2, 2.8.5.3, 2.8.5.4, 2.8.5.5, 2.8.5.6, 2.8.5.7, 2.8.5.8, 2.8.5.9, 2.8.5.10, 2.8.6.1, 2.8.6.2, 2.8.6.3, 2.8.6.4, 2.8.6.5, 2.8.6.6, 2.8.6.7, 2.8.6.8, 2.8.6.9, 2.8.6.10, 2.8.7.1, 2.8.7.2, 2.8.7.3, 2.8.7.4, 2.8.7.5, 2.8.7.6, 2.8.7.7, 2.8.7.8, 2.8.7.9, 2.8.7.10, 2.8.8.1, 2.8.8.2, 2.8.8.3, 2.8.8.4, 2.8.8.5, 2.8.8.6, 2.8.8.7, 2.8.8.8, 2.8.8.9, 2.8.8.10, 2.8.9.1, 2.8.9.2, 2.8.9.3, 2.8.9.4, 2.8.9.5, 2.8.9.6, 2.8.9.7, 2.8.9.8, 2.8.9.9, 2.8.9.10, 2.8.10.1, 2.8.10.2, 2.8.10.3, 2.8.10.4, 2.8.10.5, 2.8.10.6, 2.8.10.7, 2.8.10.8, 2.8.10.9, 2.8.10.10, 2.9.1.1, 2.9.1.2, 2.9.1.3, 2.9.1.4, 2.9.1.5, 2.9.1.6, 2.9.1.7, 2.9.1.8, 2.9.1.9, 2.9.1.10, 2.9.2.1, 2.9.2.2, 2.9.2.3, 2.9.2.4, 2.9.2.5, 2.9.2.6, 2.9.2.7, 2.9.2.8, 2.9.2.9, 2.9.2.10, 2.9.3.1, 2.9.3.2, 2.9.3.3, 2.9.3.4, 2.9.3.5, 2.9.3.6, 2.9.3.7, 2.9.3.8, 2.9.3.9, 2.9.3.10, 2.9.4.1, 2.9.4.2, 2.9.4.3, 2.9.4.4, 2.9.4.5, 2.9.4.6, 2.9.4.7, 2.9.4.8, 2.9.4.9, 2.9.4.10, 2.9.5.1, 2.9.5.2, 2.9.5.3, 2.9.5.4, 2.9.5.5, 2.9.5.6, 2.9.5.7, 2.9.5.8, 2.9.5.9, 2.9.5.10, 2.9.6.1, 2.9.6.2, 2.9.6.3, 2.9.6.4, 2.9.6.5, 2.9.6.6, 2.9.6.7, 2.9.6.8, 2.9.6.9, 2.9.6.10, 2.9.7.1, 2.9.7.2, 2.9.7.3, 2.9.7.4, 2.9.7.5, 2.9.7.6, 2.9.7.7, 2.9.7.8, 2.9.7.9, 2.9.7.10, 2.9.8.1, 2.9.8.2, 2.9.8.3, 2.9.8.4, 2.9.8.5, 2.9.8.6, 2.9.8.7, 2.9.8.8, 2.9.8.9, 2.9.8.10, 2.9.9.1, 2.9.9.2, 2.9.9.3, 2.9.9.4, 2.9.9.5, 2.9.9.6, 2.9.9.7, 2.9.9.8, 2.9.9.9, 2.9.9.10, 2.9.10.1, 2.9.10.2, 2.9.10.3, 2.9.10.4, 2.9.10.5, 2.9.10.6, 2.9.10.7, 2.9.10.8, 2.9.10.9, 2.9.10.10, 2.10.1.1, 2.10.1.2, 2.10.1.3, 2.10.1.4, 2.10.1.5, 2.10.1.6, 2.10.1.7, 2.10.1.8, 2.10.1.9, 2.10.1.10, 2.10.2.1, 2.10.2.2, 2.10.2.3, 2.10.2.4, 2.10.2.5, 2.10.2.6, 2.10.2.7, 2.10.2.8, 2.10.2.9, 2.10.2.10, 2.10.3.1, 2.10.3.2, 2.10.3.3, 2.10.3.4, 2.10.3.5, 2.10.3.6, 2.10.3.7, 2.10.3.8, 2.10.3.9, 2.10.3.10, 2.10.4.1, 2.10.4.2, 2.10.4.3, 2.10.4.4, 2.10.4.5, 2.10.4.6, 2.10.4.7, 2.10.4.8, 2.10.4.9, 2.10.4.10, 2.10.5.1, 2.10.5.2, 2.10.5.3, 2.10.5.4, 2.10.5.5, 2.10.5.6, 2.10.5.7, 2.10.5.8, 2.10.5.9, 2.10.5.10, 2.10.6.1, 2.10.6.2, 2.10.6.3, 2.10.6.4, 2.10.6.5, 2.10.6.6, 2.10.6.7, 2.10.6.8, 2.10.6.9, 2.10.6.10, 2.10.7.1, 2.10.7.2, 2.10.7.3, 2.10.7.4, 2.10.7.5, 2.10.7.6, 2.10.7.7, 2.10.7.8, 2.10.7.9, 2.10.7.10, 2.10.8.1, 2.10.8.2, 2.10.8.3, 2.10.8.4, 2.10.8.5, 2.10.8.6, 2.10.8.7, 2.10.8.8, 2.10.8.9, 2.10.8.10, 2.10.9.1, 2.10.9.2, 2.10.9.3, 2.10.9.4, 2.10.9.5, 2.10.9.6, 2.10.9.7, 2.10.9.8, 2.10.9.9, 2.10.9.10, 2.10.10.1, 2.10.10.2, 2.10.10.3, 2.10.10.4, 2.10.10.5, 2.10.10.6, 2.10.10.7, 2.10.10.8, 2.10.10.9, 2.10.10.10, 3.1.1.1, 3.1.1.2, 3.1.1.3, 3.1.1.4, 3.1.1.5, 3.1.1.6, 3.1.1.7, 3.1.1.8, 3.1.1.9, 3.1.1.10, 3.1.2.1, 3.1.2.2, 3.1.2.3, 3.1.2.4, 3.1.2.5, 3.1.2.6, 3.1.2.7, 3.1.2.8, 3.1.2.9, 3.1.2.10, 3.1.3.1, 3.1.3.2, 3.1.3.3, 3.1.3.4, 3.1.3.5, 3.1.3.6, 3.1.3.7, 3.1.3.8, 3.1.3.9, 3.1.3.10, 3.1.4.1, 3.1.4.2, 3.1.4.3, 3.1.4.4, 3.1.4.5, 3.1.4.6, 3.1.4.7, 3.1.4.8, 3.1.4.9, 3.1.4.10, 3.1.5.1, 3.1.5.2, 3.1.5.3, 3.1.5.4, 3.1.5.5, 3.1.5.6, 3.1.5.7, 3.1.5.8, 3.1.5.9, 3.1.5.10, 3.1.6.1, 3.1.6.2, 3.1.6.3, 3.1.6.4, 3.1.6.5, 3.1.6.6, 3.1.6.7, 3.1.6.8, 3.1.6.9, 3.1.6.10, 3.1.7.1, 3.1.7.2, 3.1.7.3, 3.1.7.4, 3.1.7.5, 3.1.7.6, 3.1.7.7, 3.1.7.8, 3.1.7.9, 3.1.7.10, 3.1.8.1, 3.1.8.2, 3.1.8.3, 3.1.8.4, 3.1.8.5, 3.1.8.6, 3.1.8.7, 3.1.8.8, 3.1.8.9, 3.1.8.10, 3.1.9.1, 3.1.9.2, 3.1.9.3, 3.1.9.4, 3.1.9.5, 3.1.9.6, 3.1.9.7, 3.1.9.8, 3.1.9.9, 3.1.9.10, 3.1.10.1, 3.1.10.2, 3.1.10.3, 3.1.10.4, 3.1.10.5, 3.1.10.6, 3.1.10.7, 3.1.10.8, 3.1.10.9, 3.1.10.10, 3.2.1.1, 3.2.1.2, 3.2.1.3, 3.2.1.4, 3.2.1.5, 3.2.1.6, 3.2.1.7, 3.2.1.8, 3.2.1.9, 3.2.2.1, 3.2.2.2, 3.2.2.3, 3.2.2.4, 3.2.2.5, 3.2.2.6, 3.2.2.7, 3.2.2.8, 3.2.2.9, 3.2.2.10, 3.2.3.1, 3.2.3.2, 3.2.3.3, 3.2.3.4, 3.2.3.5, 3.2.3.6, 3.2.3.7, 3.2.3.8, 3.2.3.9, 3.2.3.10,

[illegible]

[illegible]

4.8.10.2, 4.8.10.3, 4.8.10.4, 4.8.10.5, 4.8.10.6, 4.8.10.7, 4.8.10.8, 4.8.10.9, 4.8.10.10, 4.9.1.1, 4.9.1.2, 4.9.1.3, 4.9.1.4, 4.9.1.5, 4.9.1.6, 4.9.1.7, 4.9.1.8, 4.9.1.9, 4.9.1.10, 4.9.2.1, 4.9.2.2, 4.9.2.3, 4.9.2.4, 4.9.2.5, 4.9.2.6, 4.9.2.7, 4.9.2.8, 4.9.2.9, 4.9.2.10, 4.9.3.1, 4.9.3.2, 4.9.3.3, 4.9.3.4, 4.9.3.5, 4.9.3.6, 4.9.3.7, 4.9.3.8, 4.9.3.9, 4.9.3.10, 4.9.4.1, 4.9.4.2, 4.9.4.3, 4.9.4.4, 4.9.4.5, 4.9.4.6, 4.9.4.7, 4.9.4.8, 4.9.4.9, 4.9.4.10, 4.9.5.1, 4.9.5.2, 4.9.5.3, 4.9.5.4, 4.9.5.5, 4.9.5.6, 4.9.5.7, 4.9.5.8, 4.9.5.9, 4.9.5.10, 4.9.6.1, 4.9.6.2, 4.9.6.3, 4.9.6.4, 4.9.6.5, 4.9.6.6, 4.9.6.7, 4.9.6.8, 4.9.6.9, 4.9.6.10, 4.9.7.1, 4.9.7.2, 4.9.7.3, 4.9.7.4, 4.9.7.5, 4.9.7.6, 4.9.7.7, 4.9.7.8, 4.9.7.9, 4.9.7.10, 4.9.8.1, 4.9.8.2, 4.9.8.3, 4.9.8.4, 4.9.8.5, 4.9.8.6, 4.9.8.7, 4.9.8.8, 4.9.8.9, 4.9.8.10, 4.9.9.1, 4.9.9.2, 4.9.9.3, 4.9.9.4, 4.9.9.5, 4.9.9.6, 4.9.9.7, 4.9.9.8, 4.9.9.9, 4.9.9.10, 4.9.10.1, 4.9.10.2, 4.9.10.3, 4.9.10.4, 4.9.10.5, 4.9.10.6, 4.9.10.7, 4.9.10.8, 4.9.10.9, 4.9.10.10, 4.10.1.1, 4.10.1.2, 4.10.1.3, 4.10.1.4, 4.10.1.5, 4.10.1.6, 4.10.1.7, 4.10.1.8, 4.10.1.9, 4.10.1.10, 4.10.2.1, 4.10.2.2, 4.10.2.3, 4.10.2.4, 4.10.2.5, 4.10.2.6, 4.10.2.7, 4.10.2.8, 4.10.2.9, 4.10.2.10, 4.10.3.1, 4.10.3.2, 4.10.3.3, 4.10.3.4, 4.10.3.5, 4.10.3.6, 4.10.3.7, 4.10.3.8, 4.10.3.9, 4.10.3.10, 4.10.4.1, 4.10.4.2, 4.10.4.3, 4.10.4.4, 4.10.4.5, 4.10.4.6, 4.10.4.7, 4.10.4.8, 4.10.4.9, 4.10.4.10, 4.10.5.1, 4.10.5.2, 4.10.5.3, 4.10.5.4, 4.10.5.5, 4.10.5.6, 4.10.5.7, 4.10.5.8, 4.10.5.9, 4.10.5.10, 4.10.6.1, 4.10.6.2, 4.10.6.3, 4.10.6.4, 4.10.6.5, 4.10.6.6, 4.10.6.7, 4.10.6.8, 4.10.6.9, 4.10.6.10, 4.10.7.1, 4.10.7.2, 4.10.7.3, 4.10.7.4, 4.10.7.5, 4.10.7.6, 4.10.7.7, 4.10.7.8, 4.10.7.9, 4.10.7.10, 4.10.8.1, 4.10.8.2, 4.10.8.3, 4.10.8.4, 4.10.8.5, 4.10.8.6, 4.10.8.7, 4.10.8.8, 4.10.8.9, 4.10.8.10, 4.10.9.1, 4.10.9.2, 4.10.9.3, 4.10.9.4, 4.10.9.5, 4.10.9.6, 4.10.9.7, 4.10.9.8, 4.10.9.9, 4.10.9.10, 4.10.10.1, 4.10.10.2, 4.10.10.3, 4.10.10.4, 4.10.10.5, 4.10.10.6, 4.10.10.7, 4.10.10.8, 4.10.10.9, 4.10.10.10, 5.1.1.1, 5.1.1.2, 5.1.1.3, 5.1.1.4, 5.1.1.5, 5.1.1.6, 5.1.1.7, 5.1.1.8, 5.1.1.9, 5.1.1.10, 5.1.2.1, 5.1.2.2, 5.1.2.3, 5.1.2.4, 5.1.2.5, 5.1.2.6, 5.1.2.7, 5.1.2.8, 5.1.2.9, 5.1.2.10, 5.1.3.1, 5.1.3.2, 5.1.3.3, 5.1.3.4, 5.1.3.5, 5.1.3.6, 5.1.3.7, 5.1.3.8, 5.1.3.9, 5.1.3.10, 5.1.4.1, 5.1.4.2, 5.1.4.3, 5.1.4.4, 5.1.4.5, 5.1.4.6, 5.1.4.7, 5.1.4.8, 5.1.4.9, 5.1.4.10, 5.1.5.1, 5.1.5.2, 5.1.5.3, 5.1.5.4, 5.1.5.5, 5.1.5.6, 5.1.5.7, 5.1.5.8, 5.1.5.9, 5.1.5.10, 5.1.6.1, 5.1.6.2, 5.1.6.3, 5.1.6.4, 5.1.6.5, 5.1.6.6, 5.1.6.7, 5.1.6.8, 5.1.6.9, 5.1.6.10, 5.1.7.1, 5.1.7.2, 5.1.7.3, 5.1.7.4, 5.1.7.5, 5.1.7.6, 5.1.7.7, 5.1.7.8, 5.1.7.9, 5.1.7.10, 5.1.8.1, 5.1.8.2, 5.1.8.3, 5.1.8.4, 5.1.8.5, 5.1.8.6, 5.1.8.7, 5.1.8.8, 5.1.8.9, 5.1.8.10, 5.1.9.1, 5.1.9.2, 5.1.9.3, 5.1.9.4, 5.1.9.5, 5.1.9.6, 5.1.9.7, 5.1.9.8, 5.1.9.9, 5.1.9.10, 5.1.10.1, 5.1.10.2, 5.1.10.3, 5.1.10.4, 5.1.10.5, 5.1.10.6, 5.1.10.7, 5.1.10.8, 5.1.10.9, 5.1.10.10, 5.2.1.1, 5.2.1.2, 5.2.1.3, 5.2.1.4, 5.2.1.5, 5.2.1.6, 5.2.1.7, 5.2.1.8, 5.2.1.9, 5.2.1.10, 5.2.2.1, 5.2.2.2, 5.2.2.3, 5.2.2.4, 5.2.2.5, 5.2.2.6, 5.2.2.7, 5.2.2.8, 5.2.2.9, 5.2.2.10, 5.2.3.1, 5.2.3.2, 5.2.3.3, 5.2.3.4, 5.2.3.5, 5.2.3.6, 5.2.3.7, 5.2.3.8, 5.2.3.9, 5.2.3.10, 5.2.4.1, 5.2.4.2, 5.2.4.3, 5.2.4.4, 5.2.4.5, 5.2.4.6, 5.2.4.7, 5.2.4.8, 5.2.4.9, 5.2.4.10, 5.2.5.1, 5.2.5.2, 5.2.5.3, 5.2.5.4, 5.2.5.5, 5.2.5.6, 5.2.5.7, 5.2.5.8, 5.2.5.9, 5.2.5.10, 5.2.6.1, 5.2.6.2, 5.2.6.3, 5.2.6.4, 5.2.6.5, 5.2.6.6, 5.2.6.7, 5.2.6.8, 5.2.6.9, 5.2.6.10, 5.2.7.1, 5.2.7.2, 5.2.7.3, 5.2.7.4, 5.2.7.5, 5.2.7.6, 5.2.7.7, 5.2.7.8, 5.2.7.9, 5.2.7.10, 5.2.8.1, 5.2.8.2, 5.2.8.3, 5.2.8.4, 5.2.8.5, 5.2.8.6, 5.2.8.7, 5.2.8.8, 5.2.8.9, 5.2.8.10, 5.2.9.1, 5.2.9.2, 5.2.9.3, 5.2.9.4, 5.2.9.5, 5.2.9.6, 5.2.9.7, 5.2.9.8, 5.2.9.9, 5.2.9.10, 5.2.10.1, 5.2.10.2, 5.2.10.3, 5.2.10.4, 5.2.10.5, 5.2.10.6, 5.2.10.7, 5.2.10.8, 5.2.10.9, 5.2.10.10, 5.3.1.1, 5.3.1.2, 5.3.1.3, 5.3.1.4, 5.3.1.5, 5.3.1.6, 5.3.1.7, 5.3.1.8, 5.3.1.9, 5.3.1.10, 5.3.2.1, 5.3.2.2, 5.3.2.3, 5.3.2.4, 5.3.2.5, 5.3.2.6, 5.3.2.7, 5.3.2.8, 5.3.2.9, 5.3.2.10, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.3

[illegible]

[illegible]

[illegible]

7.6.9.1, 7.6.9.2, 7.6.9.3, 7.6.9.4, 7.6.9.5, 7.6.9.6, 7.6.9.7, 7.6.9.8, 7.6.9.9, 7.6.9.10, 7.6.10.1, 7.6.10.2, 7.6.10.3, 7.6.10.4, 7.6.10.5, 7.6.10.6, 7.6.10.7, 7.6.10.8, 7.6.10.9, 7.6.10.10, 7.7.1.1, 7.7.1.2, 7.7.1.3, 7.7.1.4, 7.7.1.5, 7.7.1.6, 7.7.1.7, 7.7.1.8, 7.7.1.9, 7.7.1.10, 7.7.2.1, 7.7.2.2, 7.7.2.3, 7.7.2.4, 7.7.2.5, 7.7.2.6, 7.7.2.7, 7.7.2.8, 7.7.2.9, 7.7.2.10, 7.7.3.1, 7.7.3.2, 7.7.3.3, 7.7.3.4, 7.7.3.5, 7.7.3.6, 7.7.3.7, 7.7.3.8, 7.7.3.9, 7.7.3.10, 7.7.4.1, 7.7.4.2, 7.7.4.3, 7.7.4.4, 7.7.4.5, 7.7.4.6, 7.7.4.7, 7.7.4.8, 7.7.4.9, 7.7.4.10, 7.7.5.1, 7.7.5.2, 7.7.5.3, 7.7.5.4, 7.7.5.5, 7.7.5.6, 7.7.5.7, 7.7.5.8, 7.7.5.9, 7.7.5.10, 7.7.6.1, 7.7.6.2, 7.7.6.3, 7.7.6.4, 7.7.6.5, 7.7.6.6, 7.7.6.7, 7.7.6.8, 7.7.6.9, 7.7.6.10, 7.7.7.1, 7.7.7.2, 7.7.7.3, 7.7.7.4, 7.7.7.5, 7.7.7.6, 7.7.7.7, 7.7.7.8, 7.7.7.9, 7.7.7.10, 7.7.8.1, 7.7.8.2, 7.7.8.3, 7.7.8.4, 7.7.8.5, 7.7.8.6, 7.7.8.7, 7.7.8.8, 7.7.8.9, 7.7.8.10, 7.7.9.1, 7.7.9.2, 7.7.9.3, 7.7.9.4, 7.7.9.5, 7.7.9.6, 7.7.9.7, 7.7.9.8, 7.7.9.9, 7.7.9.10, 7.7.10.1, 7.7.10.2, 7.7.10.3, 7.7.10.4, 7.7.10.5, 7.7.10.6, 7.7.10.7, 7.7.10.8, 7.7.10.9, 7.7.10.10, 7.8.1.1, 7.8.1.2, 7.8.1.3, 7.8.1.4, 7.8.1.5, 7.8.1.6, 7.8.1.7, 7.8.1.8, 7.8.1.9, 7.8.1.10, 7.8.2.1, 7.8.2.2, 7.8.2.3, 7.8.2.4, 7.8.2.5, 7.8.2.6, 7.8.2.7, 7.8.2.8, 7.8.2.9, 7.8.2.10, 7.8.3.1, 7.8.3.2, 7.8.3.3, 7.8.3.4, 7.8.3.5, 7.8.3.6, 7.8.3.7, 7.8.3.8, 7.8.3.9, 7.8.3.10, 7.8.4.1, 7.8.4.2, 7.8.4.3, 7.8.4.4, 7.8.4.5, 7.8.4.6, 7.8.4.7, 7.8.4.8, 7.8.4.9, 7.8.4.10, 7.8.5.1, 7.8.5.2, 7.8.5.3, 7.8.5.4, 7.8.5.5, 7.8.5.6, 7.8.5.7, 7.8.5.8, 7.8.5.9, 7.8.5.10, 7.8.6.1, 7.8.6.2, 7.8.6.3, 7.8.6.4, 7.8.6.5, 7.8.6.6, 7.8.6.7, 7.8.6.8, 7.8.6.9, 7.8.6.10, 7.8.7.1, 7.8.7.2, 7.8.7.3, 7.8.7.4, 7.8.7.5, 7.8.7.6, 7.8.7.7, 7.8.7.8, 7.8.7.9, 7.8.7.10, 7.8.8.1, 7.8.8.2, 7.8.8.3, 7.8.8.4, 7.8.8.5, 7.8.8.6, 7.8.8.7, 7.8.8.8, 7.8.8.9, 7.8.8.10, 7.8.9.1, 7.8.9.2, 7.8.9.3, 7.8.9.4, 7.8.9.5, 7.8.9.6, 7.8.9.7, 7.8.9.8, 7.8.9.9, 7.8.9.10, 7.8.10.1, 7.8.10.2, 7.8.10.3, 7.8.10.4, 7.8.10.5, 7.8.10.6, 7.8.10.7, 7.8.10.8, 7.8.10.9, 7.8.10.10, 7.9.1.1, 7.9.1.2, 7.9.1.3, 7.9.1.4, 7.9.1.5, 7.9.1.6, 7.9.1.7, 7.9.1.8, 7.9.1.9, 7.9.1.10, 7.9.2.1, 7.9.2.2, 7.9.2.3, 7.9.2.4, 7.9.2.5, 7.9.2.6, 7.9.2.7, 7.9.2.8, 7.9.2.9, 7.9.2.10, 7.9.3.1, 7.9.3.2, 7.9.3.3, 7.9.3.4, 7.9.3.5, 7.9.3.6, 7.9.3.7, 7.9.3.8, 7.9.3.9, 7.9.3.10, 7.9.4.1, 7.9.4.2, 7.9.4.3, 7.9.4.4, 7.9.4.5, 7.9.4.6, 7.9.4.7, 7.9.4.8, 7.9.4.9, 7.9.4.10, 7.9.5.1, 7.9.5.2, 7.9.5.3, 7.9.5.4, 7.9.5.5, 7.9.5.6, 7.9.5.7, 7.9.5.8, 7.9.5.9, 7.9.5.10, 7.9.6.1, 7.9.6.2, 7.9.6.3, 7.9.6.4, 7.9.6.5, 7.9.6.6, 7.9.6.7, 7.9.6.8, 7.9.6.9, 7.9.6.10, 7.9.7.1, 7.9.7.2, 7.9.7.3, 7.9.7.4, 7.9.7.5, 7.9.7.6, 7.9.7.7, 7.9.7.8, 7.9.7.9, 7.9.7.10, 7.9.8.1, 7.9.8.2, 7.9.8.3, 7.9.8.4, 7.9.8.5, 7.9.8.6, 7.9.8.7, 7.9.8.8, 7.9.8.9, 7.9.8.10, 7.9.9.1, 7.9.9.2, 7.9.9.3, 7.9.9.4, 7.9.9.5, 7.9.9.6, 7.9.9.7, 7.9.9.8, 7.9.9.9, 7.9.9.10, 7.9.10.1, 7.9.10.2, 7.9.10.3, 7.9.10.4, 7.9.10.5, 7.9.10.6, 7.9.10.7, 7.9.10.8, 7.9.10.9, 7.9.10.10, 7.10.1.1, 7.10.1.2, 7.10.1.3, 7.10.1.4, 7.10.1.5, 7.10.1.6, 7.10.1.7, 7.10.1.8, 7.10.1.9, 7.10.1.10, 7.10.2.1, 7.10.2.2, 7.10.2.3, 7.10.2.4, 7.10.2.5, 7.10.2.6, 7.10.2.7, 7.10.2.8, 7.10.2.9, 7.10.2.10, 7.10.3.1, 7.10.3.2, 7.10.3.3, 7.10.3.4, 7.10.3.5, 7.10.3.6, 7.10.3.7, 7.10.3.8, 7.10.3.9, 7.10.3.10, 7.10.4.1, 7.10.4.2, 7.10.4.3, 7.10.4.4, 7.10.4.5, 7.10.4.6, 7.10.4.7, 7.10.4.8, 7.10.4.9, 7.10.4.10, 7.10.5.1, 7.10.5.2, 7.10.5.3, 7.10.5.4, 7.10.5.5, 7.10.5.6, 7.10.5.7, 7.10.5.8, 7.10.5.9, 7.10.5.10, 7.10.6.1, 7.10.6.2, 7.10.6.3, 7.10.6.4, 7.10.6.5, 7.10.6.6, 7.10.6.7, 7.10.6.8, 7.10.6.9, 7.10.6.10, 7.10.7.1, 7.10.7.2, 7.10.7.3, 7.10.7.4, 7.10.7.5, 7.10.7.6, 7.10.7.7, 7.10.7.8, 7.10.7.9, 7.10.7.10, 7.10.8.1, 7.10.8.2, 7.10.8.3, 7.10.8.4, 7.10.8.5, 7.10.8.6, 7.10.8.7, 7.10.8.8, 7.10.8.9, 7.10.8.10, 7.10.9.1, 7.10.9.2, 7.10.9.3, 7.10.9.4, 7.10.9.5, 7.10.9.6, 7.10.9.7, 7.10.9.8, 7.10.9.9, 7.10.9.10, 7.10.10.1, 7.10.10.2, 7.10.10.3, 7.10.10.4, 7.10.10.5, 7.10.10.6, 7.10.10.7, 7.10.10.8, 7.10.10.9, 7.10.10.10, 8.1.1.1, 8.1.1.2, 8.1.1.3, 8.1.1.4, 8.1.1.5, 8.1.1.6, 8.1.1.7, 8.1.1.8, 8.1.1.9, 8.1.1.10, 8.1.2.1, 8.1.2.2, 8.1.2.3, 8.1.

[illegible]

[illegible]

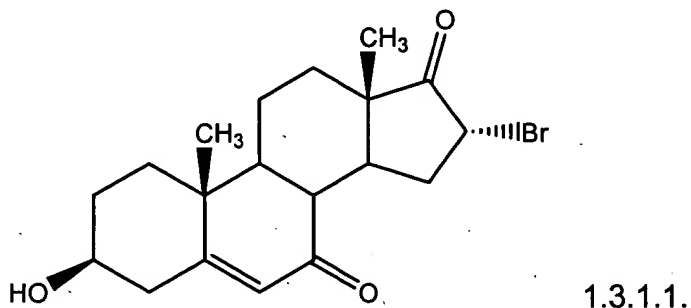
97.8.7, 97.8.8, 97.8.9, 97.8.10, 97.9.1, 97.9.2, 97.9.3, 97.9.4, 97.9.5, 97.9.6, 97.9.7, 97.9.8, 97.9.9,
97.9.10, 97.10.1, 97.10.2, 97.10.3, 97.10.4, 97.10.5, 97.10.6, 97.10.7, 97.10.8, 97.10.9, 97.10.10,
98.1.1, 98.1.2, 98.1.3, 98.1.4, 98.1.5, 98.1.6, 98.1.7, 98.1.8, 98.1.9, 98.1.10, 98.2.1, 98.2.2, 98.2.3,
98.2.4, 98.2.5, 98.2.6, 98.2.7, 98.2.8, 98.2.9, 98.2.10, 98.3.1, 98.3.2, 98.3.3, 98.3.4, 98.3.5, 98.3.6,
98.3.7, 98.3.8, 98.3.9, 98.3.10, 98.4.1, 98.4.2, 98.4.3, 98.4.4, 98.4.5, 98.4.6, 98.4.7, 98.4.8, 98.4.9,
98.4.10, 98.5.1, 98.5.2, 98.5.3, 98.5.4, 98.5.5, 98.5.6, 98.5.7, 98.5.8, 98.5.9, 98.5.10, 98.6.1, 98.6.2,
98.6.3, 98.6.4, 98.6.5, 98.6.6, 98.6.7, 98.6.8, 98.6.9, 98.6.10, 98.7.1, 98.7.2, 98.7.3, 98.7.4, 98.7.5,
98.7.6, 98.7.7, 98.7.8, 98.7.9, 98.7.10, 98.8.1, 98.8.2, 98.8.3, 98.8.4, 98.8.5, 98.8.6, 98.8.7, 98.8.8,
98.8.9, 98.8.10, 98.9.1, 98.9.2, 98.9.3, 98.9.4, 98.9.5, 98.9.6, 98.9.7, 98.9.8, 98.9.9, 98.9.10,
98.10.1, 98.10.2, 98.10.3, 98.10.4, 98.10.5, 98.10.6, 98.10.7, 98.10.8, 98.10.9, 98.10.10, 99.1.1,
99.1.2, 99.1.3, 99.1.4, 99.1.5, 99.1.6, 99.1.7, 99.1.8, 99.1.9, 99.1.10, 99.2.1, 99.2.2, 99.2.3, 99.2.4,
99.2.5, 99.2.6, 99.2.7, 99.2.8, 99.2.9, 99.2.10, 99.3.1, 99.3.2, 99.3.3, 99.3.4, 99.3.5, 99.3.6, 99.3.7,
99.3.8, 99.3.9, 99.3.10, 99.4.1, 99.4.2, 99.4.3, 99.4.4, 99.4.5, 99.4.6, 99.4.7, 99.4.8, 99.4.9, 99.4.10,
99.5.1, 99.5.2, 99.5.3, 99.5.4, 99.5.5, 99.5.6, 99.5.7, 99.5.8, 99.5.9, 99.5.10, 99.6.1, 99.6.2, 99.6.3,
99.6.4, 99.6.5, 99.6.6, 99.6.7, 99.6.8, 99.6.9, 99.6.10, 99.7.1, 99.7.2, 99.7.3, 99.7.4, 99.7.5, 99.7.6,
99.7.7, 99.7.8, 99.7.9, 99.7.10, 99.8.1, 99.8.2, 99.8.3, 99.8.4, 99.8.5, 99.8.6, 99.8.7, 99.8.8, 99.8.9,
99.8.10, 99.9.1, 99.9.2, 99.9.3, 99.9.4, 99.9.5, 99.9.6, 99.9.7, 99.9.8, 99.9.9, 99.9.10, 99.10.1,
99.10.2, 99.10.3, 99.10.4, 99.10.5, 99.10.6, 99.10.7, 99.10.8, 99.10.9, 99.10.10, 99.10.11, 99.10.12,
99.10.13, 99.10.14, 99.10.15, 99.10.16, 99.10.17, 99.10.18, 99.10.19, 99.10.10, 99.10.21, 99.10.22, 99.10.23,
99.10.24, 99.10.25, 99.10.26, 99.10.27, 99.10.28, 99.10.29, 99.10.210, 99.10.31, 99.10.32, 99.10.33, 99.10.34,
99.10.35, 99.10.36, 99.10.37, 99.10.38, 99.10.39, 99.10.310, 99.10.41, 99.10.42, 99.10.43, 99.10.44, 99.10.45,
99.10.46, 99.10.47, 99.10.48, 99.10.49, 99.10.410, 99.10.51, 99.10.52, 99.10.53, 99.10.54, 99.10.55, 99.10.56,
99.10.57, 99.10.58, 99.10.59, 99.10.510, 99.10.61, 99.10.62, 99.10.63, 99.10.64, 99.10.65, 99.10.66, 99.10.67,
99.10.68, 99.10.69, 99.10.610, 99.10.71, 99.10.72, 99.10.73, 99.10.74, 99.10.75, 99.10.76, 99.10.77, 99.10.78,
99.10.79, 99.10.710, 99.10.81, 99.10.82, 99.10.83, 99.10.84, 99.10.85, 99.10.86, 99.10.87, 99.10.88, 99.10.89,
99.10.810, 99.10.91, 99.10.92, 99.10.93, 99.10.94, 99.10.95, 99.10.96, 99.10.97, 99.10.98, 99.10.99, 99.10.910,
99.10.101, 99.10.102, 99.10.103, 99.10.104, 99.10.105, 99.10.106, 99.10.107, 99.10.108, 99.10.109, 99.10.1010,
99.10.111, 99.10.112, 99.10.113, 99.10.114, 99.10.115, 99.10.116, 99.10.117, 99.10.118, 99.10.119, 99.10.1110, 99.10.121,
99.10.122, 99.10.123, 99.10.124, 99.10.125, 99.10.126, 99.10.127, 99.10.128, 99.10.129, 99.10.1210, 99.10.131, 99.10.132,
99.10.133, 99.10.134, 99.10.135, 99.10.136, 99.10.137, 99.10.138, 99.10.139, 99.10.1310, 99.10.141, 99.10.142, 99.10.143,
99.10.144, 99.10.145, 99.10.146, 99.10.147, 99.10.148, 99.10.149, 99.10.1410, 99.10.151, 99.10.152, 99.10.153, 99.10.154,
99.10.155, 99.10.156, 99.10.157, 99.10.158, 99.10.159, 99.10.1510, 99.10.161, 99.10.162, 99.10.163, 99.10.164, 99.10.165,
99.10.166, 99.10.167, 99.10.168, 99.10.169, 99.10.1610, 99.10.171, 99.10.172, 99.10.173, 99.10.174, 99.10.175, 99.10.176,
99.10.177, 99.10.178, 99.10.179, 99.10.1710, 99.10.181, 99.10.182, 99.10.183, 99.10.184, 99.10.185, 99.10.186, 99.10.187,
99.10.188, 99.10.189, 99.10.1810, 99.10.191, 99.10.192, 99.10.193, 99.10.194, 99.10.195, 99.10.196, 99.10.197, 99.10.198,
99.10.199, 99.10.1910, 99.10.101, 99.10.102, 99.10.103, 99.10.104, 99.10.105, 99.10.106, 99.10.107, 99.10.108,
99.10.109, 99.10.1010, 99.10.111, 99.10.112, 99.10.113, 99.10.114, 99.10.115, 99.10.116, 99.10.117, 99.10.1

[illegible]

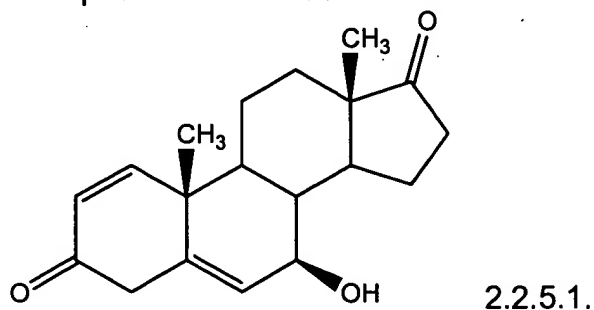
10.10.3.2, 10.10.3.3, 10.10.3.4, 10.10.3.5, 10.10.3.6, 10.10.3.7, 10.10.3.8, 10.10.3.9, 10.10.3.10, 10.10.4.1, 10.10.4.2, 10.10.4.3, 10.10.4.4, 10.10.4.5, 10.10.4.6, 10.10.4.7, 10.10.4.8, 10.10.4.9, 10.10.4.10, 10.10.5.1, 10.10.5.2, 10.10.5.3, 10.10.5.4, 10.10.5.5, 10.10.5.6, 10.10.5.7, 10.10.5.8, 10.10.5.9, 10.10.5.10, 10.10.6.1, 10.10.6.2, 10.10.6.3, 10.10.6.4, 10.10.6.5, 10.10.6.6, 10.10.6.7, 10.10.6.8, 10.10.6.9, 10.10.6.10, 10.10.7.1, 10.10.7.2, 10.10.7.3, 10.10.7.4, 10.10.7.5, 10.10.7.6, 10.10.7.7, 10.10.7.8, 10.10.7.9, 10.10.7.10, 10.10.8.1, 10.10.8.2, 10.10.8.3, 10.10.8.4, 10.10.8.5, 10.10.8.6, 10.10.8.7, 10.10.8.8, 10.10.8.9, 10.10.8.10, 10.10.9.1, 10.10.9.2, 10.10.9.3, 10.10.9.4, 10.10.9.5, 10.10.9.6, 10.10.9.7, 10.10.9.8, 10.10.9.9, 10.10.9.10, 10.10.10.1, 10.10.10.2, 10.10.10.3, 10.10.10.4, 10.10.10.5, 10.10.10.6, 10.10.10.7, 10.10.10.8, 10.10.10.9, 10.10.10.10

Additional exemplary compound groups include those disclosed below. Unless otherwise specified, the configurations of all hydrogen atoms and R groups for the following compound groups are as defined for the group 1 compounds of formula B above.

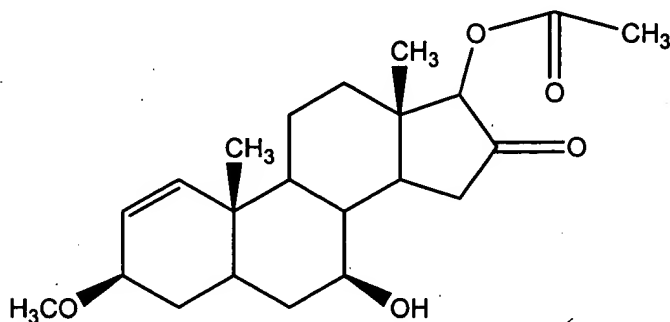
Group 2. This group comprises compounds named in Table B having R¹, R², R³ and R⁴ substituents defined in Table A wherein the R¹, R², R³ and R⁴ substituents are bonded to the steroid nucleus described for group 1 compounds, except that a double bond at the 5-6 position is present. Thus, group 2 compound 1.3.1.1 has the structure



Group 3. This group comprises compounds named in Table B having R¹, R², R³ and R⁴ substituents defined in Table A wherein the R¹, R², R³ and R⁴ substituents are bonded to the steroid nucleus as described for group 1 compounds, except that double bonds at the 1-2- and 5-6 positions are present. Thus, group 3 compound 2.2.5.1 has the structure

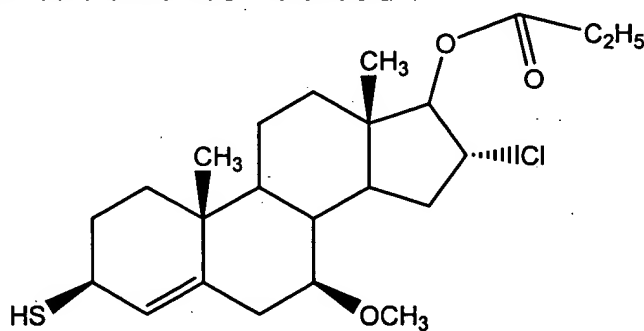


Group 4. This group comprises compounds named in Table B having R^1 , R^2 , R^3 and R^4 substituents defined in Table A wherein the R^1 , R^2 , R^3 and R^4 substituents are bonded to the steroid nucleus described for group 1 compounds, except that a double bond at the 1-2 position is present. Thus, group 4 compound 5.2.7.8 has the structure



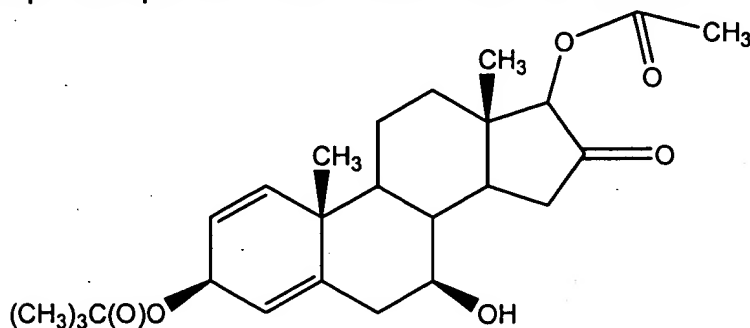
5.2.7.8.

Group 5. This group comprises compounds named in Table B having R^1 , R^2 , R^3 and R^4 substituents defined in Table A wherein the R^1 , R^2 , R^3 and R^4 substituents are bonded to the steroid nucleus described for group 1 compounds, except that a double bond at the 4-5 position is present. Thus, the group 5 compound named 3.5.2.9 has the structure



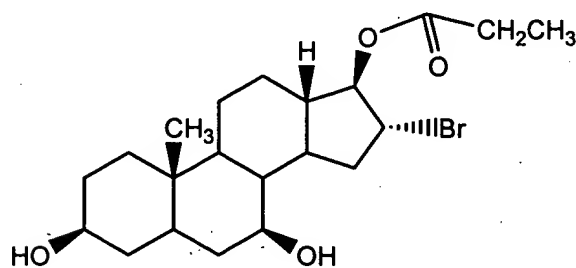
3.5.2.9.

Group 6. This group comprises compounds named in Table B having R^1 , R^2 , R^3 and R^4 substituents defined in Table A wherein the R^1 , R^2 , R^3 and R^4 substituents are bonded to the steroid nucleus described for group 1 compounds, except that double bonds at both the 1-2 and 4-5 positions are present. Thus, the group 6 compound named 10.2.7.8 has the structure

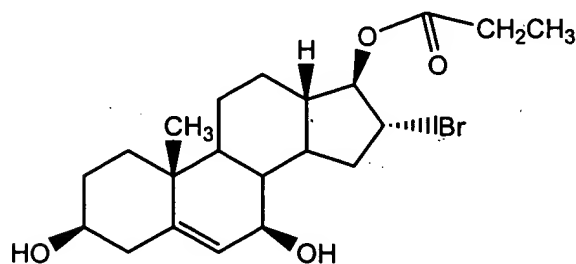


10.2.7.8.

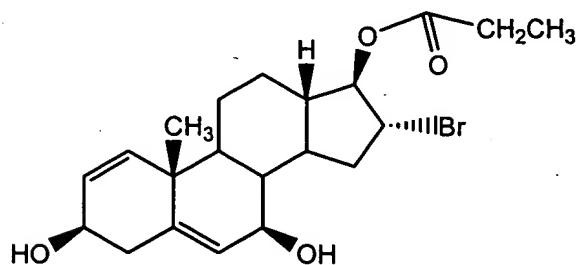
Gr ups 7-1 through 7-6. These groups comprise the 6 compound groups described above, except that R^5 is hydrogen instead of methyl. Thus, group 7-1 has the same steroid nucleus as group 1 above, i.e., no double bond is present, but R^5 is -H. Group 7-2 comprises the same steroid nucleus as group 2 above, i.e., a double bond is present at the 5-6-position, but R^5 is -H. Compound groups 7-3 through 7-6 are assigned a steroid nucleus in the same manner. Thus, the group 7-1 through group 7-6 compounds named 1.2.1.9 have the structures



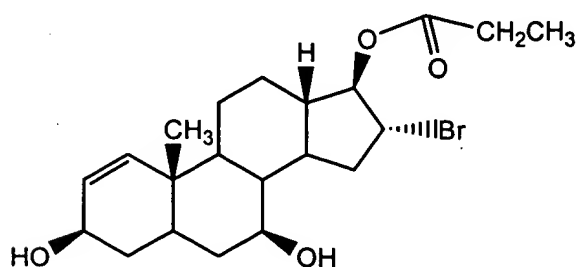
group 7-1 compound 1.2.1.9,



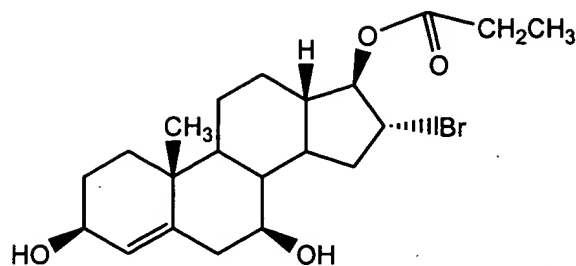
group 7-2 compound 1.2.1.9,



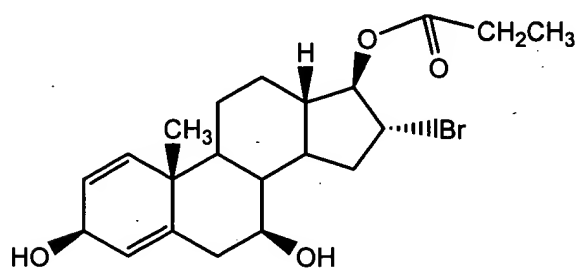
group 7-3 compound 1.2.1.9,



group 7-4 compound 1.2.1.9,

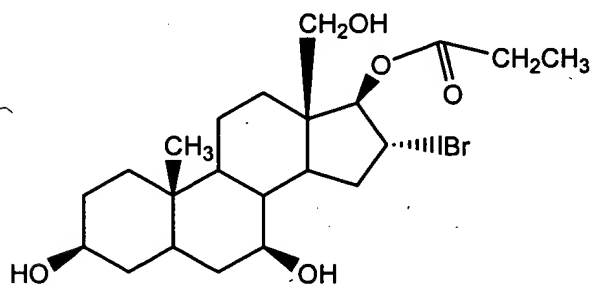


group 7-5 compound 1.2.1.9, and

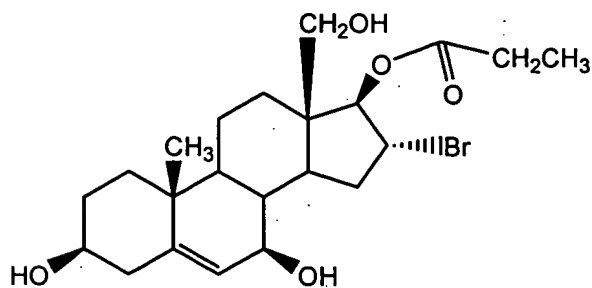


group 7-6 compound 1.2.1.9.

Groups 8-1 through 8-6. These groups comprise each compound named in groups 1-6, except that R^5 of formula B is $-\text{CH}_2\text{OH}$ instead of methyl. The groups 8-1 through group 8-6 compounds have structures that are named in the same manner as group 1-6 compounds, except that $-\text{CH}_2\text{OH}$ instead of methyl is present at R^5 . These groups are named in the same manner as groups 7-1 through 7-6. Thus, group 8-1 and group 8-2 compounds named 1.2.1.9 have the structures



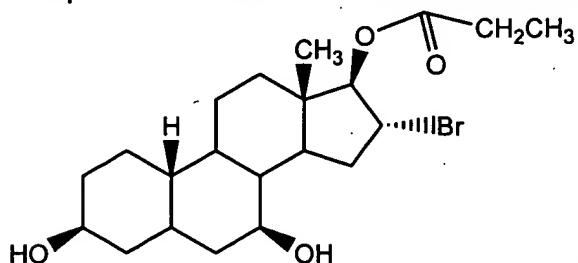
group 8-1 compound 1.2.1.9, and



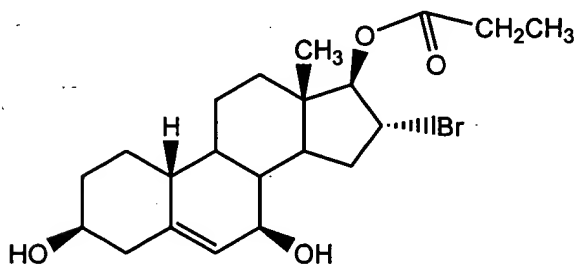
group 8-2 compound 1.2.1.9.

Groups 9-1 through 9-6. These groups comprise each compound named in compound groups 1-6, except that R^6 of formula B is hydrogen instead of methyl. The groups 9-1 through group 9-6 compounds have structures that

are named in the same manner as group 7-1 through 7-6 compounds, except that -H instead of methyl is present at R⁶. Thus, group 9-1 and group 9-2 compounds named 1.2.1.9 have the structures

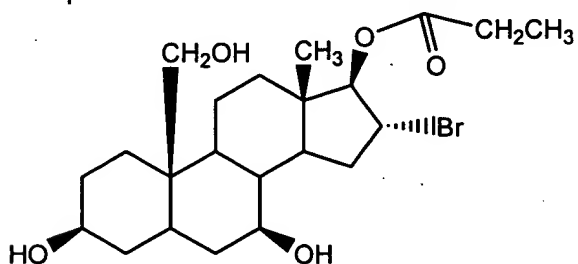


group 9-1 compound 1.2.1.9, and

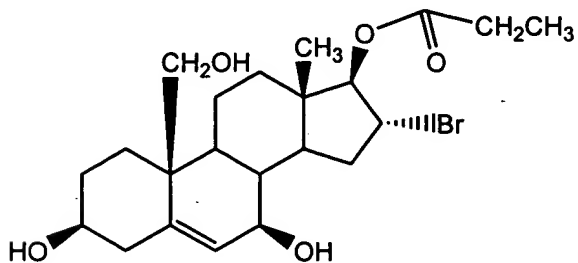


group 9-2 compound 1.2.1.9.

Groups 10-1 through 10-6. These groups comprise each compound named in compound groups 1-6 where R⁶ of formula 1 is -CH₂OH instead of methyl. The groups 10-1 through group 10-6 compounds have structures that are named in the same manner as group 7-1 through 7-6 compounds, except that -CH₂OH instead of methyl is present at R⁶. Thus, group 10-1 and group 10-2 compounds named 1.2.1.9 have the structures



group 10-1 compound 1.2.1.9, and

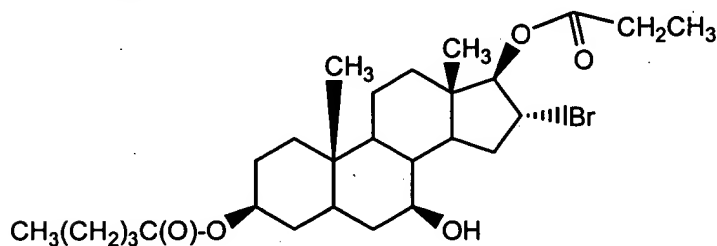


group 10-2 compound 1.2.1.9.

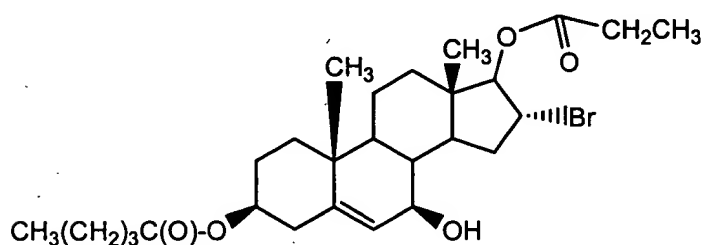
Groups 11-1 through 11-10-6. These groups comprise each compound named in compound groups 1 through 10-6 where R¹ substituents 1-10 listed in Table A are replaced with the following substituents:

- 1 -O-C(O)-CH₂CH₂CH₂CH₃ (-O-C(O)-CH₂CH₂CH₂CH₃ replaces -OH, which is R¹ substituent 1 in Table A)
- 2 -O-C(O)-CH₂CH₂CH₂CH₂CH₂CH₃
- 3 -O-C(O)-CH₂CH₂OCH₂CH₃
- 4 -O-C(O)-CH₂CH₂OCH₂CH₂OCH₂CH₃
- 5 -O-C(O)-CH₂CH₂CH₂CH₂OCH₂CH₃
- 6 -O-C(O)-CH₂CH₂OCH₂CH₂CH₂CH₃
- 7 -O-C₆H₄Cl
- 8 -O-C₆H₃F₂
- 9 -O-C₆H₄-O(CH₂)₂-O-CH₂CH₃
- 10 -O-C₆H₄-C(O)O(CH₂)₀₋₉CH₃

The group 11-1 through group 11-6 compounds have structures that are named in the same manner as group 7-1 through 7-6 compounds, except that substituents 1-10 of table A are replaced by the substituents 1-10 at R¹ listed above. Thus group 11-1 and 11-2 compounds named 1.2.1.9 have the structures

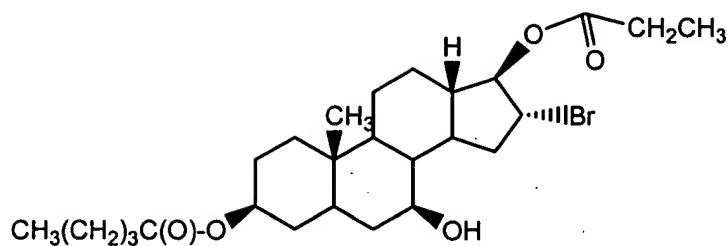


group 11-1 compound 1.2.1.9

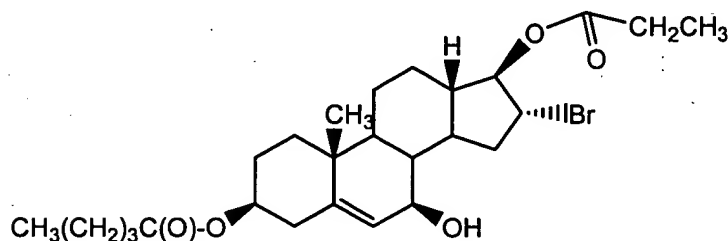


group 11-2 compound
1.2.1.9.

Group 11-7-1 and 11-7-2 compounds named 1.2.1.9 have the structures

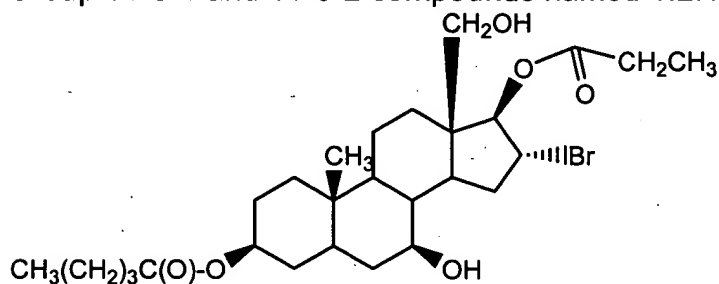


group 11-7-1 compound
1.2.1.9.

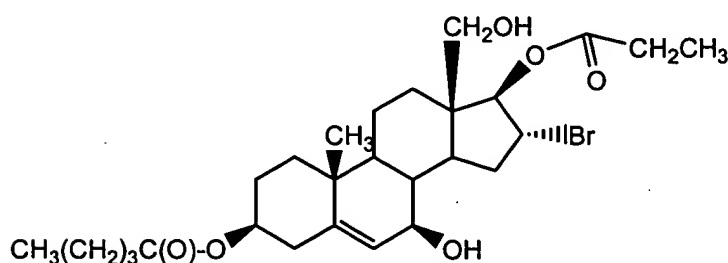


group 11-7-2 compound
1.2.1.9.

Group 11-8-1 and 11-8-2 compounds named 1.2.1.9 have the structures



group 11-8-1 compound
1.2.1.9.



group 11-8-2 compound
1.2.1.9.

Groups 12-1 through 12-10-6. These groups comprise each compound named in groups 1 through 10-6 where R¹ substituents 1-10 listed in Table A are replaced with the following groups:

- 1 -O-P(O)(O)-OCH₂CH(CH₃)CH₃ (-O-P(O)(O)-OCH₂CH(CH₃)CH₃ replaces -OH, which is R¹ substituent 1 in Table A)
- 2 -O-P(O)(O)-OCH₂CH₂CH₂CH₂CH₃
- 3 -O-P(O)(O)-OCH₂CH₂CH₂CH₂CH₂CH₃
- 4 -O-P(O)(O)-OCH₂CH₂CH(CH₂CH₂)CH₃

- 5 -O-CH₂CH₂CH₂CH₂CH₂CH₃
- 6 -O-C₂H₅
- 7 -O-CH₂CH₂CH₃
- 8 -O-CH₂CH₂CH₂CH₃
- 9 -O-CH(CH₃)CHCH₃
- 10 -O-C(CH₃)₃

Groups 13-1 through 13-10-6. These groups comprise each compound named in groups 1 through 10-6 where R¹ substituents 1-10 listed in Table A are replaced with the following groups:

- 1 -O-(CH₂)₄CH₃ (-O-(CH₂)₄CH₃ replaces -OH, which is R¹ substituent 1 in Table A)
- 2 -O-C(O)-NH₂
- 3 -O-C(O)-NHCH₃
- 4 -O-C(O)-NHC₂H₅
- 5 -O-C(O)-NHCH₂CH₂CH₃
- 6 -O-C(O)-NHCH₂CH₂OCH₂CH₃
- 7 -O-C(O)-CH₃
- 8 -O-C(O)-C₂H₅
- 9 -O-C(O)-CH₂CH₂CH₃
- 10 -O-C(O)-CH₂CH₂CH₂CH₃

Groups 14-1 through 14-10-6. These groups comprise each compound named in groups 1 through 10-6 where R¹ substituents 1-10 listed in Table A are replaced with the following groups:

- 1 -O-CH₂C₆H₅
- 2 -O-CH₂C₆H₅
- 3 -O-CH₂C₆H₄OCH₃
- 4 -O-CH₂C₆H₄OCH₃
- 5 -O-CH₂C₆H₄F
- 6 -O-CH₂C₆H₄F
- 7 -O-CH₂C₆H₃(OCH₃)₂
- 8 -O-CH₂C₆H₃(OCH₃)₂
- 9 -O-CH₂C₆H₄OCH₂CH₃
- 10 -O-CH₂C₆H₄OCH₂CH₃

Groups 15-1 through 15-10-6. These groups comprise each compound named in groups 1 through 10-6 where R¹ substituents 1-10 listed in Table A are replaced with the following groups:

- 1 -O-C(O)-CH₂CH₂NH₂ (-O-C(O)-CH₂CH₂NH₂ replaces -OH, which is R¹ substituent 1 in Table A)
- 2 -O-C(O)-CH₂CH₂CH₂NH₂
- 3 -O-C(O)-CH₂OH
- 4 -O-C(O)-CH₂CH₂OH
- 5 -O-C(O)-CH₂CH₂CH₂OH
- 6 -O-C(O)-CH₂SH
- 7 -O-C(O)-CH₂CH₂SH

- 8 -O-C(O)-CH₂CH₂CH₂SH
- 9 -O-S(O)(O)-O-CH₂-CH(O-C(O)-OH)-CH₂-O-C(O)-C₂H₅
- 10 -O-P(O)(O)-O-CH₂-CH(O-C(O)-OH)-CH₂-O-C(O)-C₂H₅

Groups 16-1 through 16-10-6. These groups comprise each compound named in groups 1 through 10-6 where R¹ substituents 1-10 listed in Table A are replaced with the following groups:

- 1 -O-C(O)-A4-NH₂, where A4-NH₂ is a 4 carbon alkyl group substituted with -NH₂ (-O-C(O)-A4-NH₂ replaces -OH, which is R¹ substituent 1 in Table A)
- 2 -O-C(O)-A6-NH₂, where A6-NH₂ is a 6 carbon alkyl group substituted with -NH₂
- 3 -O-C(O)-A8-NH₂, where A8-NH₂ is a 8 carbon alkyl group substituted with -NH₂
- 4 -O-C(O)-A4-OH, where A4-OH is a 4 carbon alkyl group substituted with -OH or -O-
- 5 -O-C(O)-A6-OH, where A6-OH is a 6 carbon alkyl group substituted with -OH or -O-
- 6 -O-C(O)-A8-OH, where A8-OH is a 8 carbon alkyl group substituted with -OH or -O-
- 7 -O-S(O)(O)-O-CH₂-CH(O-C(O)-OH)-CH₂-O-C(O)-C₃H₇
- 8 -O-P(O)(O)-O-CH₂-CH(O-C(O)-OH)-CH₂-O-C(O)-C₃H₇
- 9 -O-S(O)(O)-O-CH₂-CH(O-C(O)-OH)-CH₂-O-C(O)-C₄H₉
- 10 -O-P(O)(O)-O-CH₂-CH(O-C(O)-OH)-CH₂-O-C(O)-C₄H₉

Groups 17-1 through 17-10-6. These groups comprise each compound named in compound groups 1 through 10-6 where R¹ substituents 1-10 listed in Table A are replaced with the following groups:

- 1 -O-S(O)(O)-O-CH₂-CH(O-C(O)-OH)-CH₂-O-C(O)-C₆H₁₃
- 2 -O-P(O)(O)-O-CH₂-CH(O-C(O)-OH)-CH₂-O-C(O)-C₆H₁₃
- 3 -O-S(O)(O)-O-CH₂-CH(O-C(O)-OH)-CH₂-O-C(O)-C₈H₁₇
- 4 -O-P(O)(O)-O-CH₂-CH(O-C(O)-OH)-CH₂-O-C(O)-C₈H₁₇
- 5 -O-S(O)(O)-O-CH₂-CH(O-C(O)-OH)-CH₂-O-C(O)-CH₂C₅H₁₀OH
- 6 -O-P(O)(O)-O-CH₂-CH(O-C(O)-OH)-CH₂-O-C(O)-CH₂C₅H₁₀OH
- 7 -O-S(O)(O)-O-CH₂-CH(O-C(O)-OH)-CH₂-O-C(O)-CH₂C₃H₆OH
- 8 -O-P(O)(O)-O-CH₂-CH(O-C(O)-OH)-CH₂-O-C(O)-CH₂C₃H₆OH
- 9 -O-S(O)(O)-O-CH₂-CH(O-C(O)-OH)-CH₂-O-C(O)-CH₂C₇H₁₄OH
- 10 -O-P(O)(O)-O-CH₂-CH(O-C(O)-OH)-CH₂-O-C(O)-CH₂C₇H₁₄OH

Groups 18-1 through 18-10-6. These groups comprise each compound named in groups 1 through 10-6 where R⁴ substituents 1-10 listed in Table A are replaced with the following groups:

- 1 -O-C(O)CH₂NH₂
- 2 -O-C(O)C(CH₃)H-NH₂
- 3 -O-C(O)C(CH₂C₆H₅)H-NH₂
- 4 -O-C(O)-O-NHC(CH₃)H-CO₂H
- 5 -O-C(O)-O-NHCH₂-CO₂H

- 6 -O-C(O)-O-NH(CH₂C₆H₅)H-CO₂H
- 7 -O-C(O)-CF₃
- 8 -O-C(O)-CH₂CF₃
- 9 -O-C(O)-(CH₂)₃CF₃
- 10 -O-C(O)-(CH₂)₅CH₃

Groups 19-1 through 19-10-6. These groups comprise each compound named in compound groups 1 through 10-6 where R⁴ substituents 1-10 listed in Table A are replaced with the following groups:

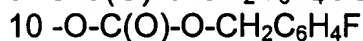
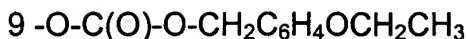
- 1 -O-C(O)-O-CH₃
- 2 -O-C(O)-O-CH₂CH₃
- 3 -O-C(O)-O-C₃H₇
- 4 -O-C(O)-O-C₄H₉
- 5 -O-C(O)-O-C₆H₁₃
- 6 -O-C(O)-O-C₆H₅
- 7 -O-C(O)-O-C₆H₄OH
- 8 -O-C(O)-O-C₆H₄OCH₃
- 9 -O-C(O)-O-C₆H₄OCH₂CH₃
- 10 -O-C(O)-O-C₆H₄F

Groups 20-1 through 20-10-6. These groups comprise each compound named in groups 1 through 10-6 where R⁴ substituents 1-10 listed in Table A are replaced with the following groups:

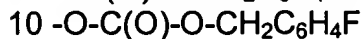
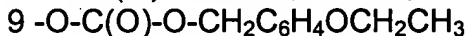
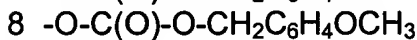
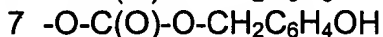
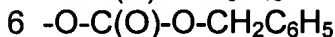
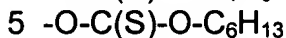
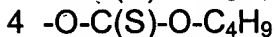
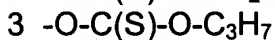
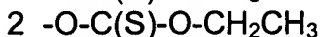
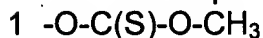
- 1 -O-C(O)-S-CH₃
- 2 -O-C(O)-S-CH₂CH₃
- 3 -O-C(O)-S-C₃H₇
- 4 -O-C(O)-S-C₄H₉
- 5 -O-C(O)-S-C₆H₁₃
- 6 -O-C(O)-S-C₆H₅
- 7 -O-C(O)-S-C₆H₄OH
- 8 -O-C(O)-S-C₆H₄OCH₃
- 9 -O-C(O)-S-C₆H₄OCH₂CH₃
- 10 -O-C(O)-S-C₆H₄F

Groups 21-1 through 21-10-6. These groups comprise each compound named in compound groups 1 through 10-6 where R⁴ substituents 1-10 listed in Table A are replaced with the following groups:

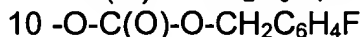
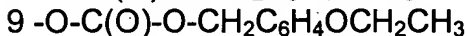
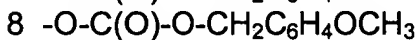
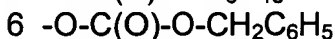
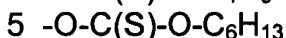
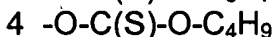
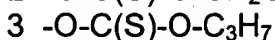
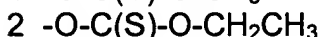
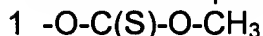
- 1 -O-C(S)-O-CH₃
- 2 -O-C(S)-O-CH₂CH₃
- 3 -SH
- 4 =S
- 5 -O-C(S)-O-C₆H₁₃
- 6 -O-C(O)-O-CH₂C₆H₅
- 7 -O-C(O)-O-CH₂C₆H₄OH
- 8 -O-C(O)-O-CH₂C₆H₄OCH₃



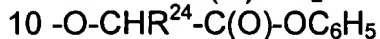
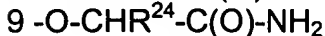
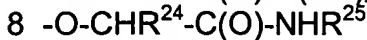
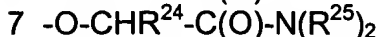
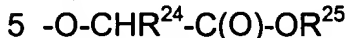
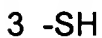
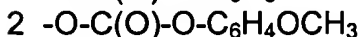
Groups 22-1 through 22-10-6. These groups comprise each compound named in compound groups 1 through 10-6 where R² substituents 1-10 listed in Table A are replaced with the following groups:



Groups 23-1 through 23-10-6. These groups comprise each compound named in compound groups 1 through 10-6 where R³ substituents 1-10 listed in Table A are replaced with the following groups:



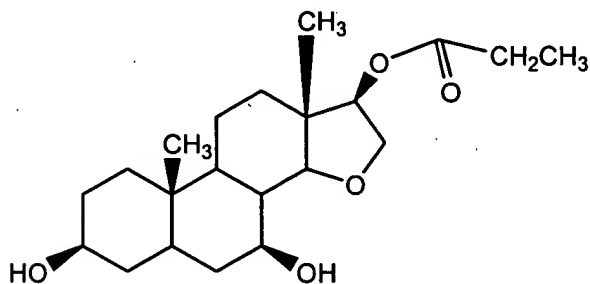
Groups 24-1 through 24-10-6. These groups comprise each compound named in compound groups 1 through 10-6 where R² substituents 1-10 listed in Table A are replaced with the following groups:



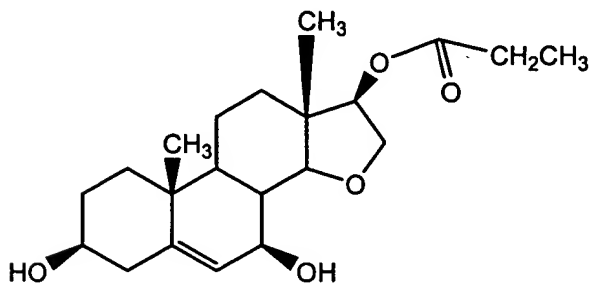
Groups 25-1 through 25-10-6. These groups comprise each compound named in compound groups 1 through 10-6 where R^3 substituents 1-10 listed in Table A are replaced with the following groups:

- 1 -O-C(O)-O-C₆H₅
- 2 -O-C(O)-O-C₆H₄OCH₃
- 3 -SH
- 4 =S
- 5 -O-CHR²⁴-C(O)-OR²⁵
- 6 -O-CHR²⁴-C(O)-R²⁵
- 7 -O-CHR²⁴-C(O)-N(R²⁵)₂
- 8 -O-CHR²⁴-C(O)-NHR²⁵
- 9 -O-CHR²⁴-C(O)-NH₂
- 10 -O-CHR²⁴-C(O)-OC₆H₅.

Groups 26-1 through 26-25-10-6. These groups comprise each compound named in compound groups 1 through 25-10-6 wherein R^7 in formula B is -O-, instead of -CH₂-. Thus the 26-1 and 26-2 compounds named 1.2.5.9 have the structures

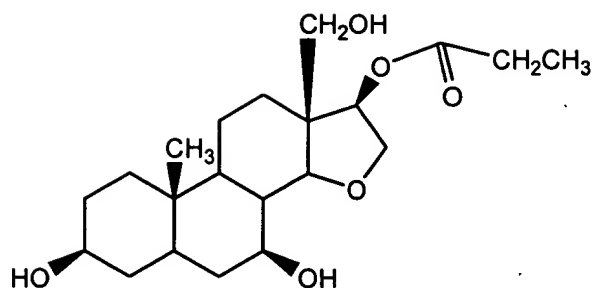


group 26-1 compound 1.2.5.9, and

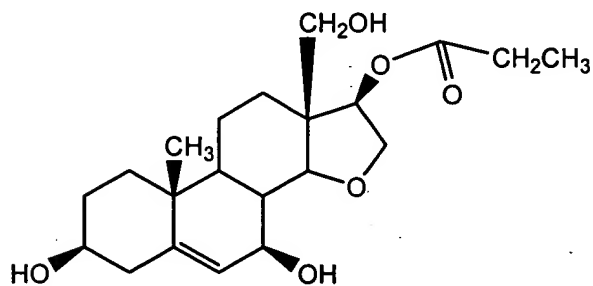


group 26-2 compound 1.2.5.9.

The compound group 26-8-1 and compound group 26-8-2 compounds named 1.2.5.9 have the structures

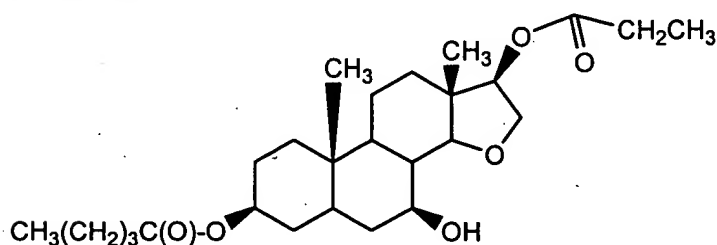


group 26-8-1 compound 1.2.5.9, and

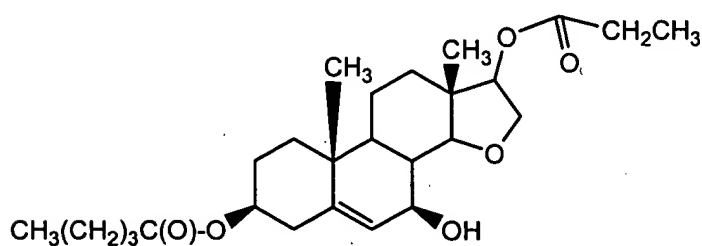


group 26-8-2 compound 1.2.5.9.

The group 26-11-1 and 26-11-2 compounds named 1.2.5.9 have the structures



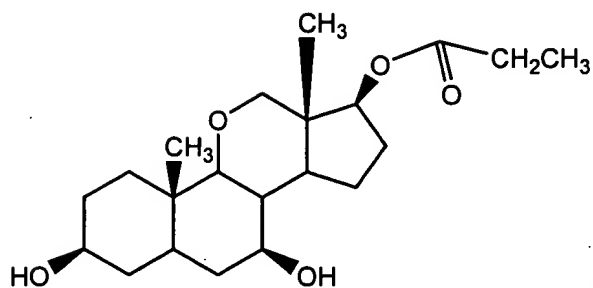
group 26-11-1 compound
1.2.5.9



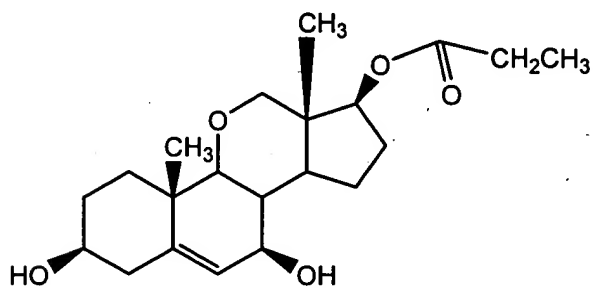
group 26-11-2 compound

1.2.5.9.

Groups 27-1 through 27-25-10-6. These groups comprise each compound named in compound groups 1 through 25-10-6 wherein R^8 in formula B is -O-, instead of -CH₂-. Thus the 27-1 and 27-2 compounds named 1.2.5.9 have the structures

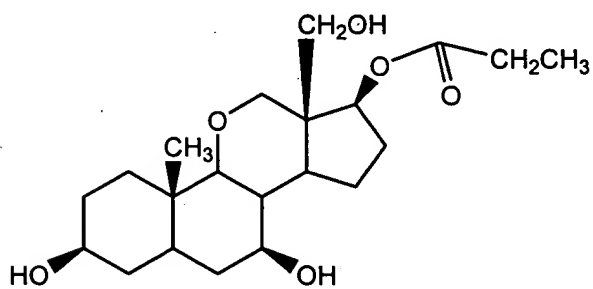


group 27-1 compound 1.2.5.9, and

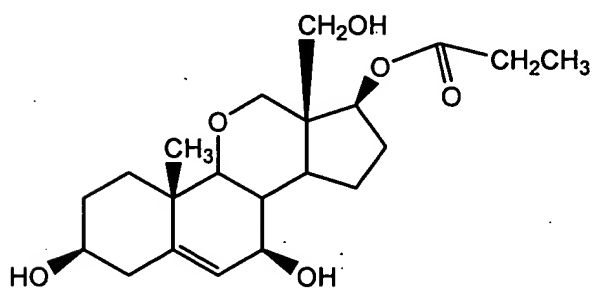


group 27-2 compound 1.2.5.9.

The group 27-8-1 and group 27-8-2 compounds named 1.2.5.9 have the structures

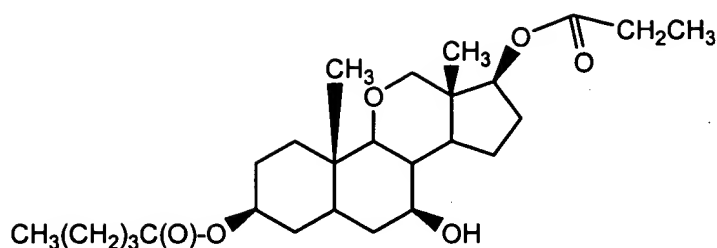


group 27-8-1 compound 1.2.5.9, and

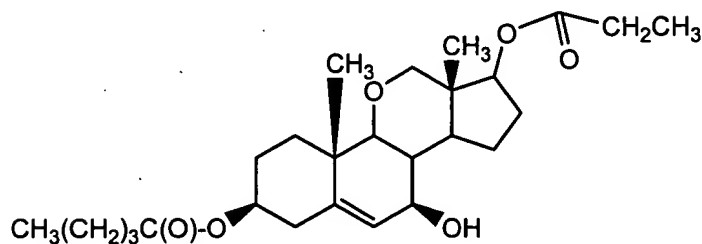


group 27-8-2 compound 1.2.5.9.

The group 27-11-1 and 27-11-2 compounds named 1.2.5.9 have the structures

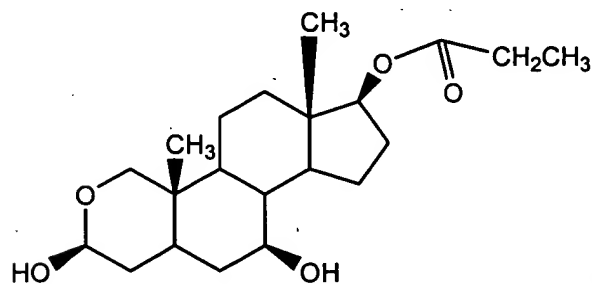


group 27-11-1 compound
1.2.5.9

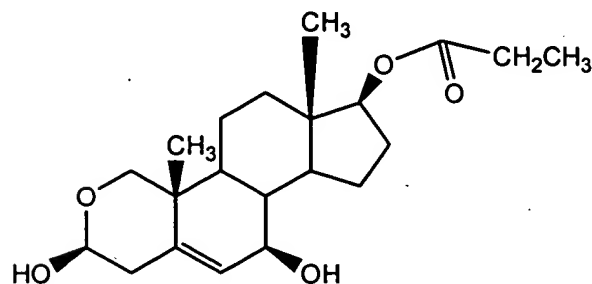


group 27-11-2 compound
1.2.5.9.

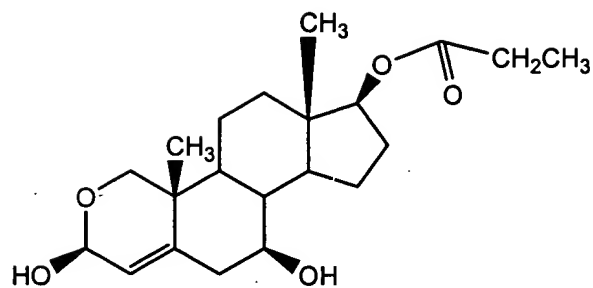
Groups 28-1 through 28-25-10-6. These groups comprise each compound named in compound groups 1 through 25-10-6 wherein R⁹ in formula B is -O-, instead of -CH₂- and no double bond is present at the 1-2 position. Thus, there is, e.g., no group 28-3, 28-4, 28-6, 28-8-3, 28-8-4 or 28-8-6, since a 1-2 double bond is present in these compounds and a ring oxygen at the 2 position would be charged. The 28-1, 28-2 and 28-5 compounds named 1.2.5.9 have the structures



group 28-1 compound 1.2.5.9, and

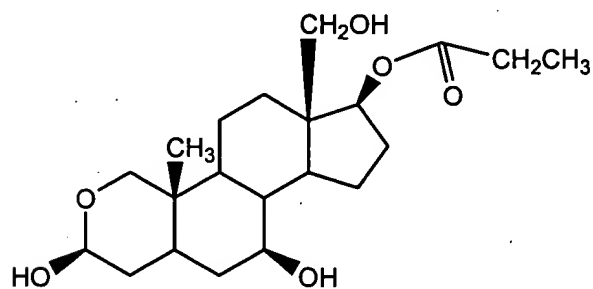


group 28-2 compound 1.2.5.9

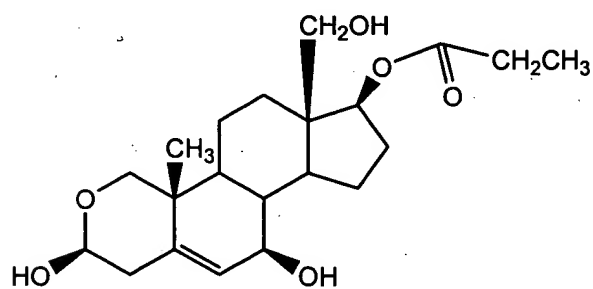


group 28-5 compound 1.2.5.9.

The group 28-8-1 and group 28-8-2 compounds named 1.2.5.9 have the structures

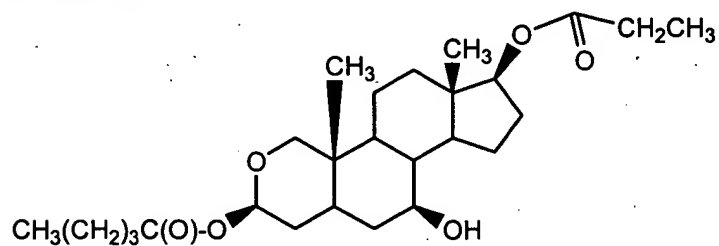


group 28-8-1 compound 1.2.5.9, and

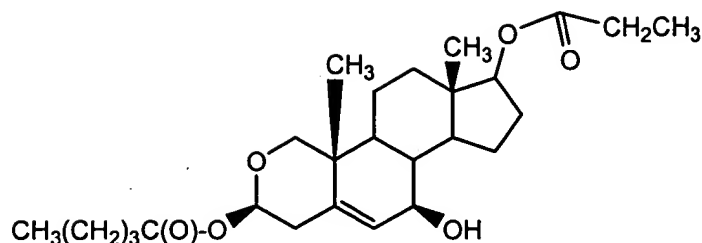


group 28-8-2 compound 1.2.5.9.

The group 28-11-1 and 28-11-2 compounds named 1.2.5.9 have the structures



group 28-11-1 compound
1.2.5.9



group 28-11-2 compound
1.2.5.9.

Groups 29-1 through 29-25-10-6. These groups comprise each compound named in compound groups 1 through 25-10-6 wherein R⁷ is -NH-, instead of -CH₂-. The compounds are named as described for compound groups 26-1 through 26-25-10-6.

Groups 30-1 through 30-25-10-6. These groups comprise each compound named in compound groups 1 through 25-10-6 wherein R⁸ is -NH-, instead of -CH₂-. The compounds are named as described for compound groups 26-1 through 26-25-10-6.

Groups 31-1 through 31-25-10-6. These groups comprise each compound named in compound groups 1 through 25-10-6 wherein R⁹ is -NH-, instead of -CH₂-, and no double bond is present at the 1-2 position. Thus, there is , e.g., no group 31-3, 31-4, 31-6, 31-8-3, 31-8-4 or 31-8-6. The compounds are named as described for compound groups 26-1 through 26-25-10-6.

Groups 32-1 through 32-25-10-6. These groups comprise each compound named in compound groups 1 through 25-10-6 wherein two of R⁷ R⁸ and R⁹ independently are -NH-, -O- or -S- instead of -CH₂-. The compounds are named as described for compound groups 26-1 through 26-25-10-6.

Groups 33-1 through 33-25-10-6. These groups comprise each compound named in compound groups 1 through 25-10-6 wherein each of R⁷ R⁸ and R⁹ independently are -NH-, -O- or -S- instead of -CH₂-. The compounds are named as described for compound groups 26-1 through 26-25-10-6.

Groups 34-1 through 34-25-10-6. These groups comprise each compound named in compound groups 1 through 25-10-6 wherein R⁷ is -S-, instead of -CH₂-. The compounds are named as described for compound groups 26-1 through 26-25-10-6.

Groups 35-1 through 35-25-10-6. These groups comprise each compound named in compound groups 1 through 25-10-6 wherein R^8 is -S-, instead of -CH₂-. The compounds are named as described for compound groups 26-1 through 26-25-10-6.

Groups 36-1 through 36-25-10-6. These groups comprise each compound named in compound groups 1 through 25-10-6 wherein R^9 is -S-, instead of -CH₂- and no double bond is present at the 1-2 position. There is , e.g., no group 36-3, 36-4, 36-6, 36-8-3, 36-8-4 or 36-8-6. The compounds are named as described for compound groups 26-1 through 26-25-10-6.

Groups 37-1 through 37-25-10-6. These groups comprise each compound named in all of the compound compound groups 1 through 36-25-10-6 described above wherein R^1 is not divalent, e.g., is not =O, and it is in the α -configuration, instead of the β -configuration as shown in formula B.

Groups 38-1 through 38-25-10-6. These groups comprise each compound named in all of the compound groups 1 through 36-25-10-6 described above wherein R^2 is not divalent, e.g., is not =O, and it is in the α -configuration, instead of the β -configuration as shown in formula B.

Groups 39-1 through 39-25-10-6. These groups comprise each compound named in all of the compound groups 1 through 36-25-10-6 described above wherein R^3 is not divalent, e.g., is not =O, and it is in the β -configuration, instead of the α -configuration as shown in formula B.

Groups 40-1 through 40-25-10-6. These groups comprise each compound named in all of the compound groups 1 through 36-25-10-6 described above wherein R^4 is not divalent, e.g., is not =O, and it is in the α -configuration, instead of the β -configuration as shown in formula B. These are thus exemplary formula 2 compounds.

Groups 41-1 through 41-25-10-6. These groups comprise each compound named in all of the compound groups 1 through 36-25-10-6 described above wherein R^2 and R^4 is not divalent, e.g., they is not =O, and they are both in the α -configuration, instead of the β -configuration as shown in formula B.

Groups 42-1 through 42-25-10-6. These groups comprise each compound named in all of the compound groups 1 through 36-25-10-6 described above wherein, when hydrogen is present at the 5-position, it is in the β -configuration, instead of the α -configuration as shown in formula B.

Any of the compounds or genera of compounds that are named in compound groups 1 through 42-25-10-6 are suitable for use in the methods and treating the conditions described herein or in the cited references.

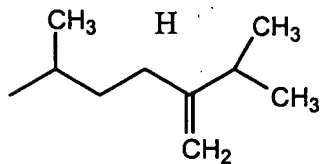
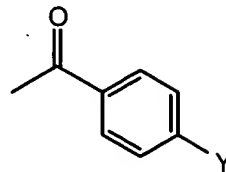
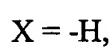
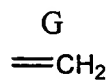
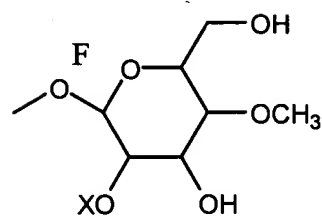
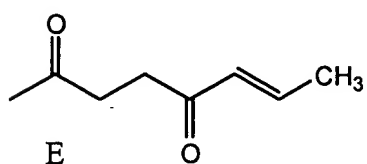
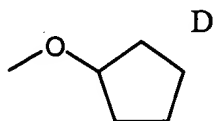
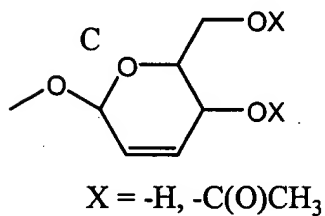
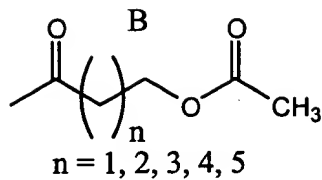
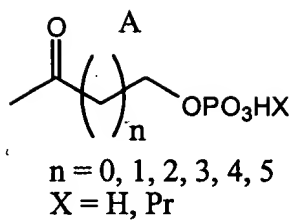
In some embodiments, one, or more of R^1 - R^6 , R^{10} , R^{15} , R^{17} and R^{18} independently have the structure(s) and/or independently comprise the named compounds, -H, -OH, =O, -SH, =S, -NH₂, -CN, -N₃, halogen, =CH₂, =NOH, =NOC(O)CH₃, -C(O)-CH₃, -C(O)-(CH₂)₁₋₄-CH₃, -CCH, -CCCH₃, -CH=CH₂, -CH=CH₂CH₃, -O-C(O)-(CH₂)_m-(CF₂)_n-CH₃, -O-C(O)-(CH₂)_m-(CF₂)_n-CF₃, -O-C(O)-(CH₂)_m-(CF₂)_n-CH₂F, -O-C(O)-O-(CH₂)_m-(CF₂)_n-CH₃, -O-C(O)-O-(CH₂)_m-(CF₂)_n-CF₃, -O-C(O)-O-(CH₂)_m-(CF₂)_n-CH₂F, -O-C(O)-NH-(CH₂)_m-(CF₂)_n-CH₃, -O-C(O)-NH-(CH₂)_m-(CF₂)_n-CF₃, -O-C(O)-NH-(CH₂)_m-(CF₂)_n-CH₂F (where m is 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, usually n is 0), -CH(CH₃)-(CH₂)₂-C(O)NH-CH₂COOH, -CH(CH₃)-(CH₂)₂-C(O)NH-CH₂SO₃H, -OSi(CH₃)₂C(CH₃)₃, -C(OH)=CHCH₃, =CH(CH₂)₀₋₁₅CH₃, -(CH₂)₀₋₁₄CH₂F, -(CH₂)₀₋₁₄CH₂Cl, -(CH₂)₀₋₁₄CH₂Br, -(CH₂)₀₋₁₄CH₂I, -(CH₂)₂₋₁₀-O-(CH₂)₀₋₄CH₃, -(CH₂)₂₋₁₀-S-(CH₂)₀₋₄CH₃, -(CH₂)₂₋₁₀-NH-(CH₂)₀₋₄CH₃, -O-(CH₂)₀₋₁₄CH₂F, -O-(CH₂)₀₋₁₄CH₂Cl, -O-(CH₂)₀₋₁₄CH₂Br, -O-(CH₂)₀₋₁₄CH₂I, -O-(CH₂)₂₋₁₀-O-(CH₂)₀₋₄CH₃, -O-(CH₂)₂₋₁₀-S-(CH₂)₀₋₄CH₃, -O-(CH₂)₂₋₁₀-NH-(CH₂)₀₋₄CH₃, -O-C(O)-(CH₂)₀₋₁₄CH₂F, -O-C(O)-(CH₂)₀₋₁₄CH₂Cl, -O-C(O)-(CH₂)₀₋₁₄CH₂Br, -O-C(O)-(CH₂)₀₋₁₄CH₂I, -O-C(O)-(CH₂)₂₋₁₀-O-(CH₂)₀₋₄CH₃, -O-C(O)-(CH₂)₂₋₁₀-S-(CH₂)₀₋₄CH₃, -O-C(O)-(CH₂)₂₋₁₀-NH-(CH₂)₀₋₄CH₃, -O-C(S)-(CH₂)₀₋₁₄CH₂F, -O-C(S)-(CH₂)₀₋₁₄CH₂Cl, -O-C(S)-(CH₂)₀₋₁₄CH₂Br, -O-C(S)-(CH₂)₀₋₁₄CH₂I, -O-C(S)-(CH₂)₂₋₁₀-O-(CH₂)₀₋₄CH₃, -O-C(S)-(CH₂)₂₋₁₀-S-(CH₂)₀₋₄CH₃, -O-C(S)-(CH₂)₂₋₁₀-NH-(CH₂)₀₋₄CH₃, -(CH₂)₀₋₁₆NH₂, -(CH₂)₀₋₁₅CH₃, -(CH₂)₀₋₁₅CN, -(CH₂)₀₋₁₅CH=CH₂, -(CH₂)₀₋₁₅NHCH(O), -(CH₂)₀₋₁₆NH-(CH₂)₀₋₁₅CH₃, -(CH₂)₀₋₁₅CCH, -(CH₂)₀₋₁₅OC(O)CH₃, -(CH₂)₀₋₁₅OCH(OH)CH₃, -(CH₂)₀₋

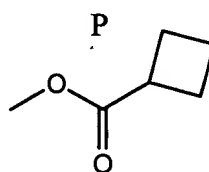
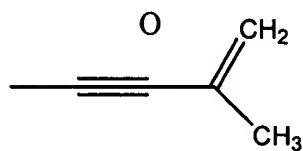
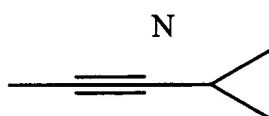
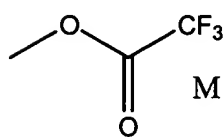
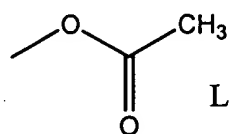
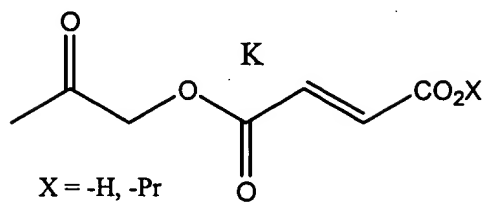
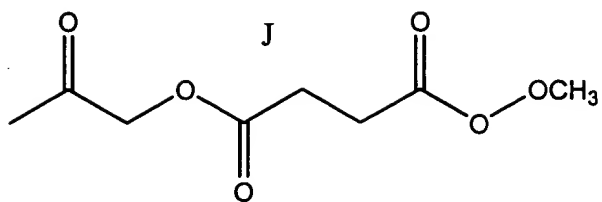
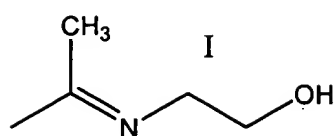
$_{15}\text{C}(\text{O})\text{OCH}_3$, $-(\text{CH}_2)_{0-15}\text{C}(\text{O})\text{OCH}_2\text{CH}_3$, $-(\text{CH}_2)_{0-15}\text{C}(\text{O})(\text{CH}_2)_{0-15}\text{CH}_3$, $-(\text{CH}_2)_{0-15}\text{C}(\text{O})(\text{CH}_2)_{0-15}\text{CH}_2\text{OH}$, $-\text{O}(\text{CH}_2)_{1-16}\text{NH}_2$, $-\text{O}(\text{CH}_2)_{1-15}\text{CH}_3$, $-\text{O}(\text{CH}_2)_{1-15}\text{CN}$, $-\text{O}(\text{CH}_2)_{1-15}\text{CH}=\text{CH}_2$, $-\text{O}(\text{CH}_2)_{1-15}\text{NHCH}(\text{O})$, $-\text{O}(\text{CH}_2)_{1-16}\text{NH}-(\text{CH}_2)_{1-15}\text{CH}_3$, $-\text{O}(\text{CH}_2)_{1-15}\text{CCH}$, $-\text{O}(\text{CH}_2)_{1-15}\text{OC}(\text{O})\text{CH}_3$, $-\text{O}(\text{CH}_2)_{1-15}\text{OCH}(\text{OH})\text{CH}_3$, $-\text{O}(\text{CH}_2)_{1-15}\text{C}(\text{O})\text{OCH}_3$, $-\text{O}(\text{CH}_2)_{1-15}\text{C}(\text{O})\text{OCH}_2\text{CH}_3$, $-\text{O}(\text{CH}_2)_{1-15}\text{C}(\text{O})(\text{CH}_2)_{0-15}\text{CH}_3$, $-\text{O}(\text{CH}_2)_{1-15}\text{C}(\text{O})(\text{CH}_2)_{0-15}\text{CH}_2\text{OH}$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-16}\text{NH}_2$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-15}\text{CH}_3$, $-\text{C}(\text{O})\text{O}(\text{CH}_2)_{1-15}\text{CN}$, $-\text{C}(\text{O})\text{O}(\text{CH}_2)_{1-15}\text{CH}=\text{CH}_2$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-15}\text{NHCH}(\text{O})$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-16}\text{NH}-(\text{CH}_2)_{1-15}\text{CH}_3$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-15}\text{CCH}$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-15}\text{OC}(\text{O})\text{CH}_3$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-15}\text{OCH}(\text{OH})\text{CH}_3$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-15}\text{C}(\text{O})\text{OCH}_3$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-15}\text{C}(\text{O})\text{OCH}_2\text{CH}_3$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-15}\text{C}(\text{O})(\text{CH}_2)_{0-15}\text{CH}_3$, $-\text{OC}(\text{O})(\text{CH}_2)_{1-15}\text{C}(\text{O})(\text{CH}_2)_{0-15}\text{CH}_2\text{OH}$, phosphoenolpyruvate, D-glucosamine, glucolic acid, glucuronic acid, pantothenic acid, pyruvic acid, glucose, fructose, mannose, sucrose, lactose, fucose, rhamnose, galactose, ribose, 2'-deoxyribose, 3'-deoxyribose, glycerol, 3-phosphoglycerate, a PEG (PEG 20, PEG 100, PEG 200, PEG 10000), a polyoxyalkylene polymer, glycine, alanine, phenylalanine, threonine, proline or 4-hydroxyproline.

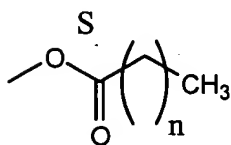
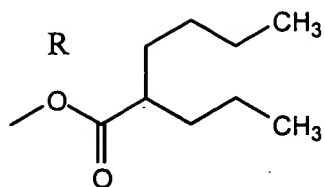
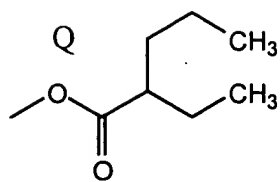
When a substituent is a polymer usually only a one of these is bonded to the formula 1 compound. Typically, when R^1 - R^2 and R^4 - R^6 comprise one or more of these substituents (or others described herein), the substituent is present in the β -configuration, while R^3 typically comprises a substituent in the β -configuration. In some embodiments, R^2 is in the α -configuration.

Table 2 shows exemplary moieties that one or more of R^1 - R^6 , R^{10} , R^{15} , R^{17} and R^{18} independently can comprise. Pr means a protecting group. These moieties are often bonded to one or more of the R^1 , R^2 and R^4 positions, usually to one or two of those positions. For structures with more than one of a given variable, e.g., X in structure A3 or A5, each is independently selected.

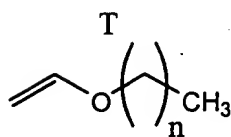
TABLE 2



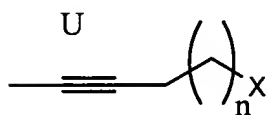




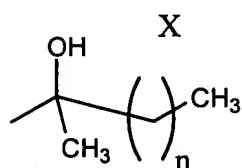
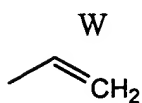
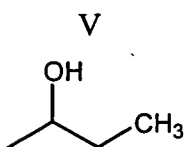
$n = 1, 2, 3, 4, 5, 6$



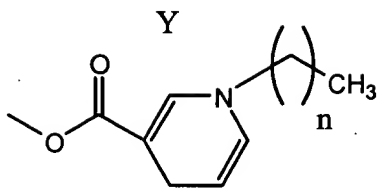
$n = 1, 2, 3, 4, 5, 6$



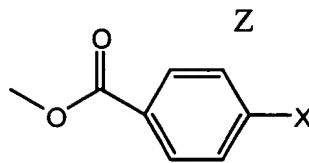
$n = 0, 1, 2, 3, 4, 5, 6$
 $X = \text{CH}_3, \text{Cl}$



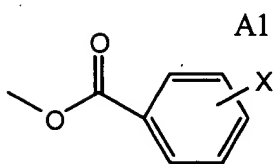
$n = 0, 1, 2, 3, 4, 5, 6$



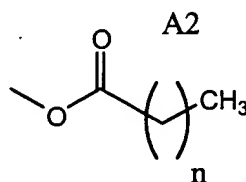
$n = 0, 1, 2, 3, 4, 5, 6$



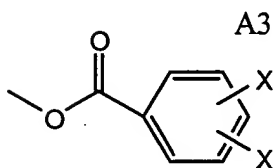
$X = F, Cl, Br, NO_2, OCH_3, OC_2H_5, CN$



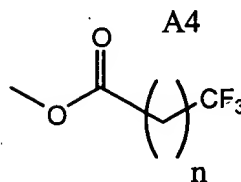
$X = H, F, Cl, Br, NO_2, OCH_3, OC_2H_5, CN$



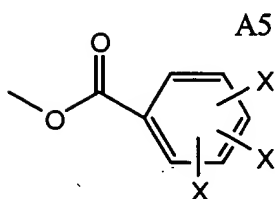
$n = 1, 2, 3, 4, 5, 6$



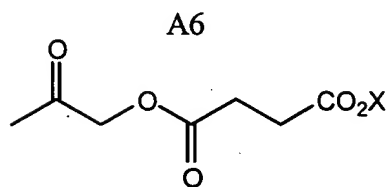
$X = H, F, Cl, Br, NO_2, OCH_3, OC_2H_5, CN$



$n = 0, 1, 2, 3, 4, 5, 6$

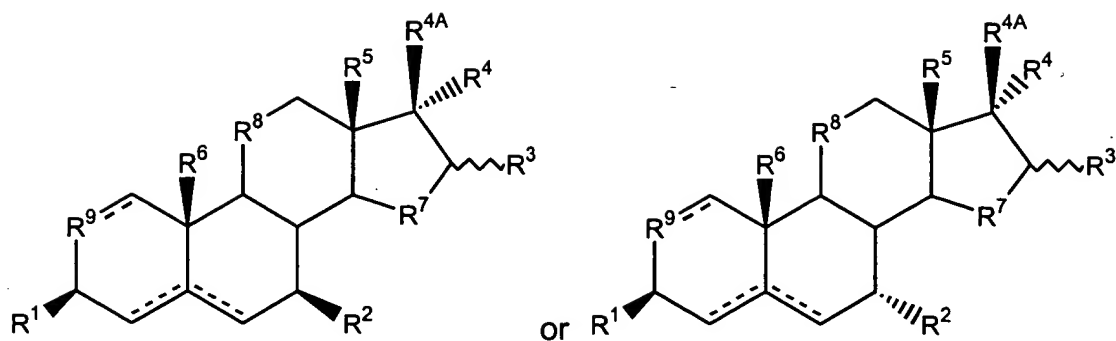


$X = H, F, Cl, Br, NO_2, OCH_3, OC_2H_5, CN$

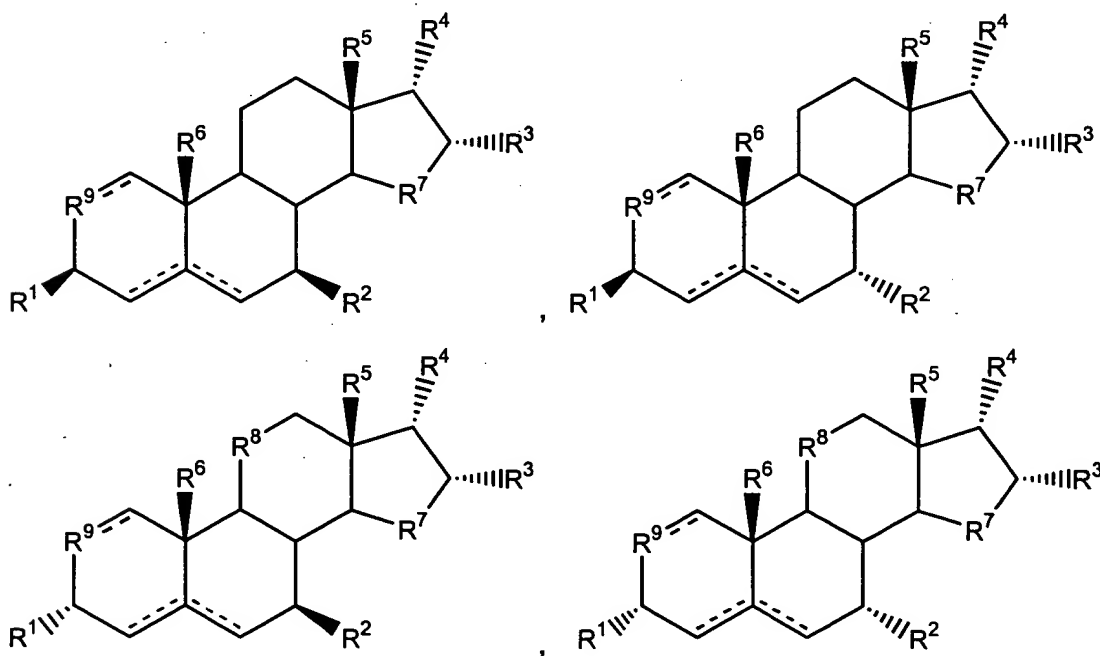


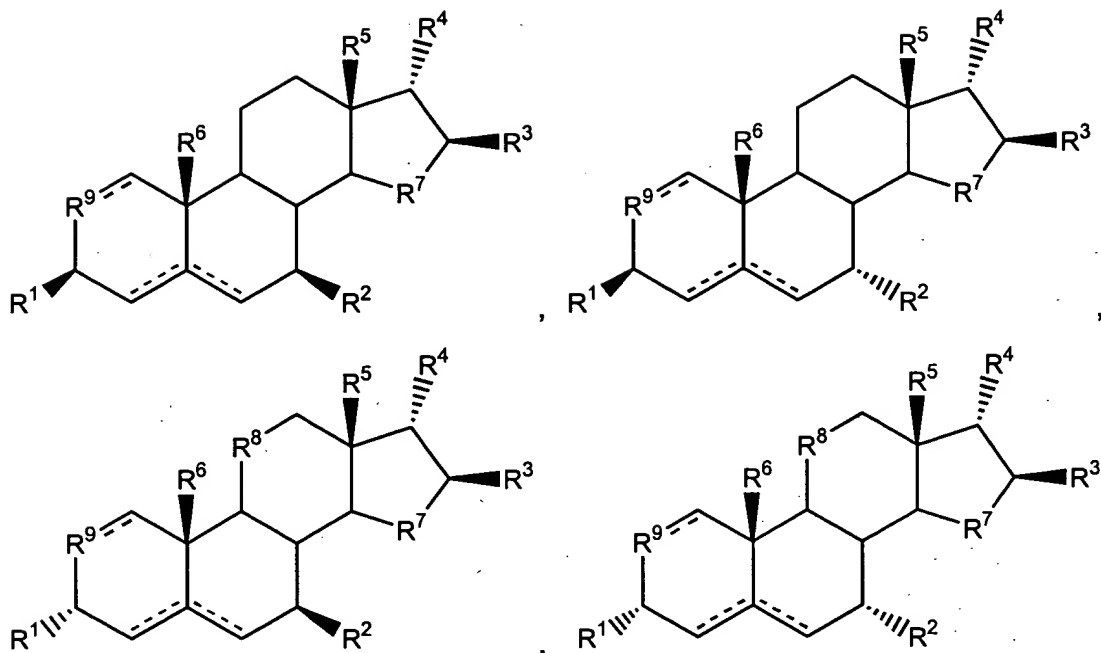
$X = H, Pr$

In some embodiments, the formula 1 compound has the structure



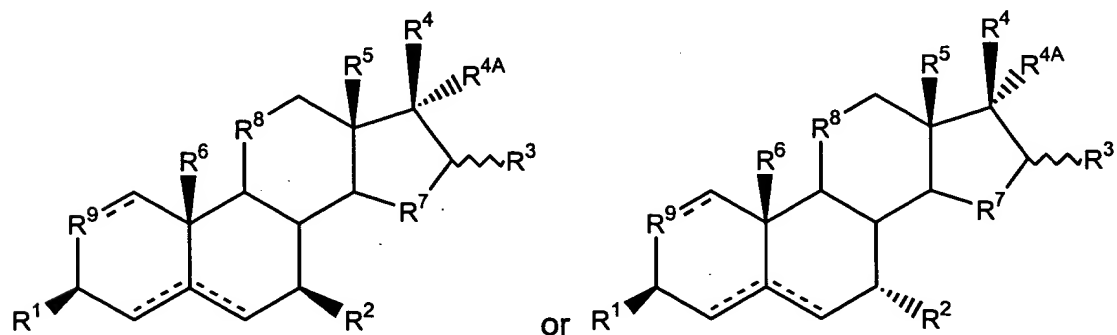
wherein R^{4A} is -H, -CH₃, -C₂H₅ or a halogen, R^7 and R^9 independently are -CHR¹⁰-, -CH₂-, -CH=, -O-, -S- or -NH-, wherein R^{10} is -OH, -SH, C₁₋₁₀ optionally substituted alkyl, C₁₋₁₀ optionally substituted alkoxy and R^8 is -CH₂-, -O-, -S- or -NH-, wherein hydrogen atoms at the 5 (if present), 8, 9 and 14 positions respectively are $\alpha.\alpha.\alpha.\alpha$ (i.e., 5 α , 8 α , 9 α , 14 α), $\alpha.\alpha.\alpha.\beta$, $\alpha.\alpha.\beta.\alpha$, $\alpha.\beta.\alpha.\alpha$, $\beta.\alpha.\alpha.\alpha$, $\alpha.\alpha.\beta.\beta$, $\alpha.\beta.\alpha.\beta$, $\beta.\alpha.\alpha.\beta$, $\beta.\alpha.\beta.\alpha$, $\beta.\beta.\alpha.\alpha$, $\alpha.\beta.\beta.\alpha$, $\alpha.\beta.\beta.\beta$, $\beta.\alpha.\beta.\beta$, $\beta.\beta.\alpha.\beta$, $\beta.\beta.\beta.\alpha$ or $\beta.\beta.\beta.\beta$, typically $\alpha.\alpha.\beta.\alpha$ or $\beta.\alpha.\beta.\alpha$. These compounds include compounds having the structure





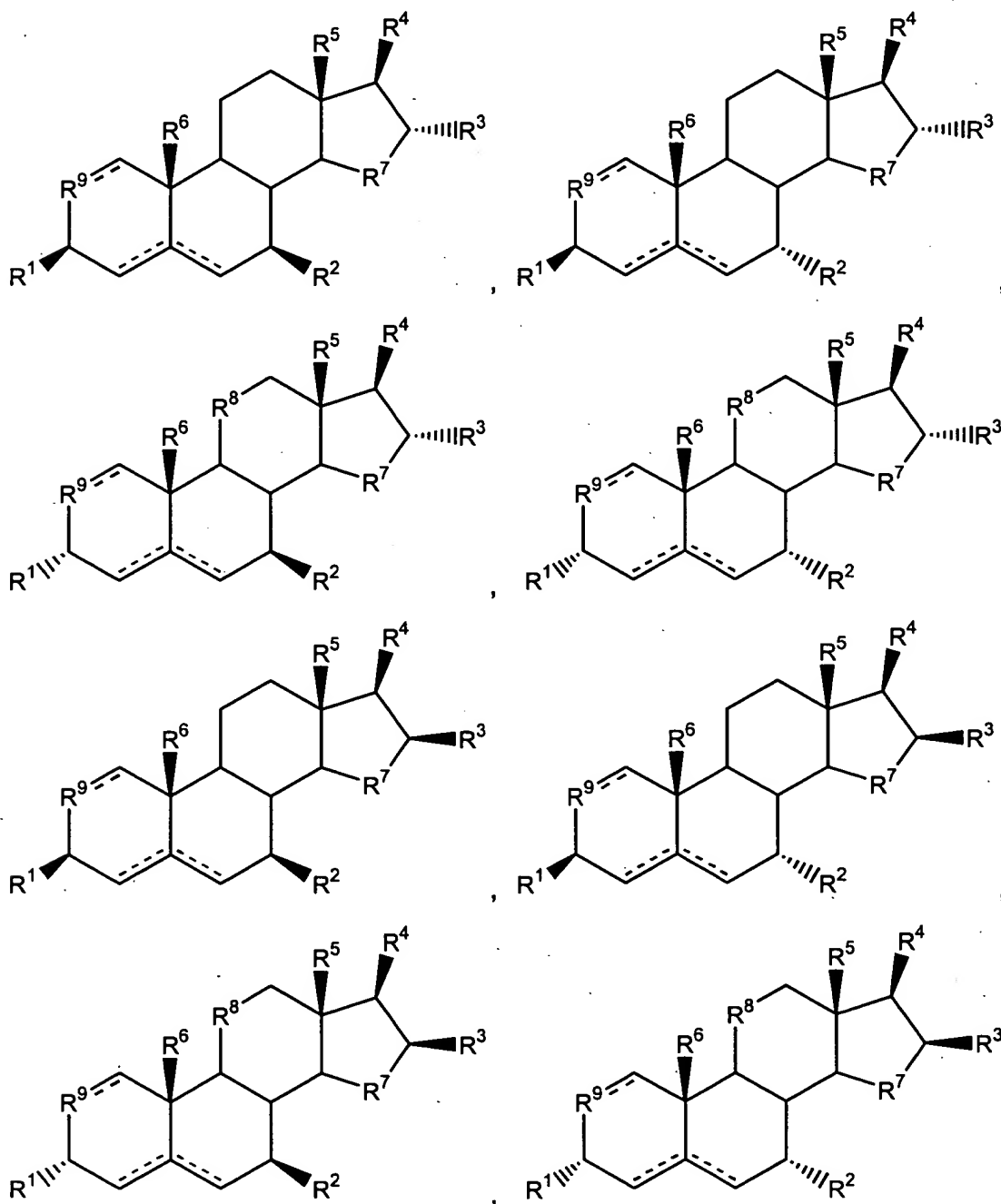
wherein hydrogen atoms at the 5 (if present), 8, 9 and 14 positions respectively are $\alpha.\alpha.\alpha.\alpha$, $\alpha.\alpha.\alpha.\beta$, $\alpha.\alpha.\beta.\alpha$, $\alpha.\beta.\alpha.\alpha$, $\beta.\alpha.\alpha.\alpha$, $\alpha.\alpha.\beta.\beta$, $\alpha.\beta.\alpha.\beta$, $\beta.\alpha.\alpha.\beta$, $\beta.\alpha.\beta.\alpha$, $\beta.\beta.\alpha.\alpha$, $\alpha.\beta.\beta.\alpha$, $\alpha.\beta.\beta.\beta$, $\beta.\alpha.\beta.\beta$, $\beta.\beta.\alpha.\beta$, $\beta.\beta.\beta.\alpha$ or $\beta.\beta.\beta.\beta$, typically $\alpha.\alpha.\beta.\alpha$ or $\beta.\alpha.\beta.\alpha$. In these embodiments, R^1 and R^2 may independently be -OH, -SH, -OR^{PR}, an ester, an ether, a thioester, a thioether or another moiety as disclosed herein, R^3 may be -H, -F, -Cl, -Br, -I, optionally substituted alkyl or another moiety as disclosed herein and R^4 optionally is -OH, -SH or a moiety that can convert to -OH or -SH by metabolism or by hydrolysis, e.g., a moiety as defined herein.

In some embodiments, the formula 2 compound has the structure



wherein R^{4A} is -H, -CH₃, -C₂H₅ or a halogen, R^7 and R^9 independently are -CHR¹⁰-, -CH₂-, -CH=, -O-, -S- or -NH-, wherein R^{10} is -OH, -SH, C₁₋₁₀ optionally substituted alkyl, C₁₋₁₀ optionally substituted alkoxy and R^8 is -CH₂-, -O-, -S- or -

NH-, wherein hydrogen atoms at the 5 (if present), 8, 9 and 14 positions respectively are $\alpha.\alpha.\alpha.\alpha$ (i.e., $5\alpha, 8\alpha, 9\alpha, 14\alpha$), $\alpha.\alpha.\alpha.\beta$, $\alpha.\alpha.\beta.\alpha$, $\alpha.\beta.\alpha.\alpha$, $\beta.\alpha.\alpha.\alpha$, $\alpha.\alpha.\beta.\beta$, $\alpha.\beta.\alpha.\beta$, $\beta.\alpha.\alpha.\beta$, $\beta.\alpha.\beta.\alpha$, $\beta.\beta.\alpha.\alpha$, $\alpha.\beta.\beta.\alpha$, $\alpha.\beta.\beta.\beta$, $\beta.\alpha.\beta.\beta$, $\beta.\beta.\alpha.\beta$, $\beta.\beta.\beta.\alpha$ or $\beta.\beta.\beta.\beta$, typically $\alpha.\alpha.\beta.\alpha$ or $\beta.\alpha.\beta.\alpha$. These compounds include compounds having the structure



wherein hydrogen atoms at the 5 (if present), 8, 9 and 14 positions respectively are $\alpha.\alpha.\alpha.\alpha$, $\alpha.\alpha.\alpha.\beta$, $\alpha.\alpha.\beta.\alpha$, $\alpha.\beta.\alpha.\alpha$, $\beta.\alpha.\alpha.\alpha$, $\alpha.\alpha.\beta.\beta$, $\alpha.\beta.\alpha.\beta$, $\beta.\alpha.\alpha.\beta$, $\beta.\alpha.\beta.\alpha$,

$\beta.\beta.\alpha.\alpha$, $\alpha.\beta.\beta.\alpha$, $\alpha.\beta.\beta.\beta$, $\beta.\alpha.\beta.\beta$, $\beta.\beta.\alpha.\beta$, $\beta.\beta.\beta.\alpha$ or $\beta.\beta.\beta.\beta$, typically $\alpha.\alpha.\beta.\alpha$ or $\beta.\alpha.\beta.\alpha$. In these embodiments, R^4 may be -OH, =O, -SH, a C_{1-30} ester or C_{1-30} alkoxy, wherein the ester or alkoxy moiety is optionally substituted with one, two or more independently selected substituents, which are optionally selected from -F, -Cl, -Br, -I, -O-, =O, -S-, -NH-, -OR^{PR}, -SR^{PR} or -NHR^{PR}. Also, in these embodiments, R^1 and R^2 may independently optionally be -OH, -SH, -OR^{PR}, an ester, an ether, a thioester, a thioether or another moiety as disclosed herein, R^3 optionally is -H, -F, -Cl, -Br, -I, optionally substituted alkyl or another moiety as disclosed herein and R^4 optionally is -OH, -SH or a moiety that can convert to -OH or -SH by metabolism or by hydrolysis, e.g., a moiety as defined herein.